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Utility of cerebral proton magnetic resonance spectroscopy in differential diagnosis of HIV-related dementia

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Opportunistic infections often coexist with human immunodeficiency virus (HIV) infection in brain. Making the correct diagnosis is often difficult despite recent advances in neuroimaging techniques. ^{1}H magnetic resonance spectroscopy (^{1}H MRS) is an emerging non-invasive examination for diagnosis and monitoring of brain disorders. ^{1}H MRS measures a variety of organic compounds using magnetism and radio waves. Biochemical aberrations in brain, not shown by conventional tests, may be demonstrated by ^{1}H MRS testing. A patient coinfected with HIV and hepatititis B (HBV) presented with progressive dementia. Clinical, neuroradiological and cerebrospinal fluid (CSF) examinations failed to provide a diagnosis in support of either HIV-1- associated cognitive/motor complex or HBV-induced hepatic encephalopathy (HE). ^{1}H MRS was used in an attempt to discriminate between these diagnoses. Spectroscopy demonstrated increased glutamine and normal N-acetyl aspartate (NAA) levels, metabolic changes consistent with HE. These findings were later confirmed pathologically. Proton magnetic resonance spectroscopy is a non-invasive test with utility for the differential diagnosis of HIV-associated dementia.

Keywords: HIV brain infection; AIDS dementia complex; hepatitis B; hepatic encephalopathy; magnetic resonance spectroscopy

Introduction

Neurological dysfunction is a common complication of HIV disease. Autopsy studies have shown pathologic abnormalities in the central nervous system of 75 to 90% of patients with the acquired immunodeficiency syndrome (AIDS) (Snider, Simpson *et al*, 1983; Levy, Bredesen *et al*, 1985). An extraordinarily wide spectrum of neurological disorders can occur. These fall into four general categories: primary HIV infection of the brain, opportunistic infection by bacteria, viruses, fungi or parasites, CNS neoplasms, or complications of systemic disease. Importantly, HIV often affects brain function directly causing an encephalopathy. HIV-1-associated cognitive/motor complex (also known as AIDS dementia complex or HIV encephalopathy) remains the most common central nervous system (CNS) complication of HIV infection.

Differential diagnosis of neurological dysfunction in the HIV-infected patient is difficult, and multiple neurological diseases may coexist within the same patient. Neuroimaging techniques have revolutionized the diagnosis of neurological disorders during recent years. Since Bloch and Purcell independently discovered nuclear magnetic resonance (NMR) in 1946, the scientific applications of this technology have greatly expanded (Bloch and Hansen, 1946; Purcell and Torrey 1946). Magnetic resonance imaging (MRI) was adapted for use in humans during the 1980s and now has widespread use in medical diagnosis. Nevertheless, this technology often fails to detect subtle metabolic or function alterations of the brain. ^{1}H MRS is currently entering a stage of clinical development as MRI was in the 1980s, and can be performed on a conventional clinical MRI

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with specialized hardware to acquire and interpret spectroscopy. By delineating the *in vivo* pathobiochemical changes in the brain, magnetic resonance spectroscopy (MRS) has an important role in the diagnosis and monitoring of neurological diseases. Indeed, ^{1}H MRS has already been used to demonstrate biochemical changes in various degenerative, demyelinating, vascular and neoplastic disorders of the CNS (Husted, 1994; Barker *et al*, 1994; Connelly *et al*, 1994).

^{1}H MRS holds considerable potential in the differential diagnosis of HIV-related neurological disorders. Primary infection of the brain by HIV can be particularly difficult to diagnose, as significant pathologic changes are often absent. Neuronal loss is a common finding in brain tissue of patients with HIV-1-associated cognitive/motor complex (Giangaspero *et al*, 1989; Wiley *et al*, 1991; Everall *et al*, 1991). NAA, a metabolite largely confined to neurons, can be readily detected in the brain by ^{1}H MRS (Miller, 1991). Preliminary clinical studies suggest that NAA can be used as a non-invasive assessment of neuronal loss. A decreased brain NAA to creatine (CR) or choline (CHO) ratio has been shown to correlate with progressive neurological impairment in patients with HIV-1-associated cognitive/motor complex (Cohen *et al*, 1992; Chong *et al*, 1993; Jerrigan *et al*, 1993; Meyerhoff *et al*, 1993; McConnell *et al*, 1994).

Recent ^{1}H MRS studies have found abnormal concentrations of brain metabolites in patients with HE (Bosman *et al*, 1990; Kreis *et al*, 1992; McConnell *et al*, 1993). HE is a common neurological complication of liver failure, and as many as 72% of patients with cirrhosis and portal hypertension have been found to have HE on psychometric testing (Schomerus *et al*, 1993). The ^{1}H MRS pathobiochemical findings of HE include elevated glutamine (GLN), decreased inositol (INS) and decreased CHO peak intensities (Kreis *et al*, 1992; McConnell, 1995, in press). Increased brain GLN appears to play an important role in the pathogenesis of HE, possibly contributing to the development of brain edema. Concurrently, brain myoinositol and CHO containing compounds are decreased, creating a characteristic pathobiochemical pattern of metabolites. (Kreis *et al*, 1992; McConnell, 1995, in press). The CHO resonances represent a group of membrane precursors including free choline, phosphocholine, glyceryl phosphocholine and acetylcholine.

Both transmitted parenterally and sexually, HIV and HBV frequently coexist. Up to 96% of HIV-infected individuals have serologic evidence of prior HBV infection (Rogers *et al*, 1983).

Importantly, both HIV and HBV can cause progressive cognitive and motor impairment, culminating in coma and death. Despite diverse pathologies, clinical manifestations of HIV-1-associated cognitive/motor complex and HE can be similar. There is no diagnostic test for either syndrome. When both HIV and HBV coexist and neurologic impairment is present, differential diagnosis of cognitive and motor dysfunction can be challenging.

In order to differentiate HIV-1-associated cognitive/motor complex and HE, we utilized ^{1}H MRS of the brain in an HIV-1 infected patient with chronic active hepatitis B and progressive dementia. The pathobiochemical changes of HE were found on *in vivo* ^{1}H MRS, and later confirmed by histopathology at post-mortem examination.

Results

A 45-year-old white HIV-1 seropositive male with chronic active hepatitis B was admitted to hospital following an episode of syncope. He had a history of portal hypertension with esophageal varices, and had experienced three prior episodes of gastrointestinal bleeding. One month prior to admission, he had undergone transhepatic intravenous portal systemic shunting (TIPS).

The patient had been diagnosed with HIV-1 infection in 1989, and with AIDS on the basis of a low CD4+ lymphocyte count in 1993. The most recent CD+ lymphocyte count was 86 cells mm^3. He had no history of significant opportunistic infection or malignancy, with the exception of severe thrombocytopenia refractory to treatment.

He complained of headache and constipation. On evaluation, he was alert, oriented and without postural hypotension or other abnormal physical findings. His mental status examination was within normal limits. Neurological examination demonstrated normal cranial nerve function, strength and reflexes. No asterixis or milk-maid's grip was noted. Platelet count was 17,000 mm^3 and the patient received a platelet transfusion. A lumbar puncture was performed. Cerebrospinal fluid (CSF) protein was 60 mg dl and glucose 53 mg dl. CSF cell count showed 4075 red blood cells mm^3 and four white blood cells mm^3 of which 67% were polymorphonuclear cells and 30% were lymphocytes. Bacterial, mycobacterial, fungal and viral cultures were negative. CSF glutamine was 3400.9 UM L (70–890 UM L). MRI of the brain was performed, and revealed a small posterior fossa subdural hematoma extending to the distal thecal sac. There was no obstruction or displacement of the fourth ventricle, or hydrocephalus. There was no supratentorial hemorrhage, and the hematoma was not thought to be contributing to the clinical condition.

Over a period of days, the patient's mental status declined markedly. He became disoriented to time and place. Differential diagnosis included subdural hematoma, hepatic encephalopathy, HIV-1-associated cognitive/motor complex, or some combination of these diagnoses. He was treated with lactulose for what was thought to be HE with only slight improvement. On further decline of his mental

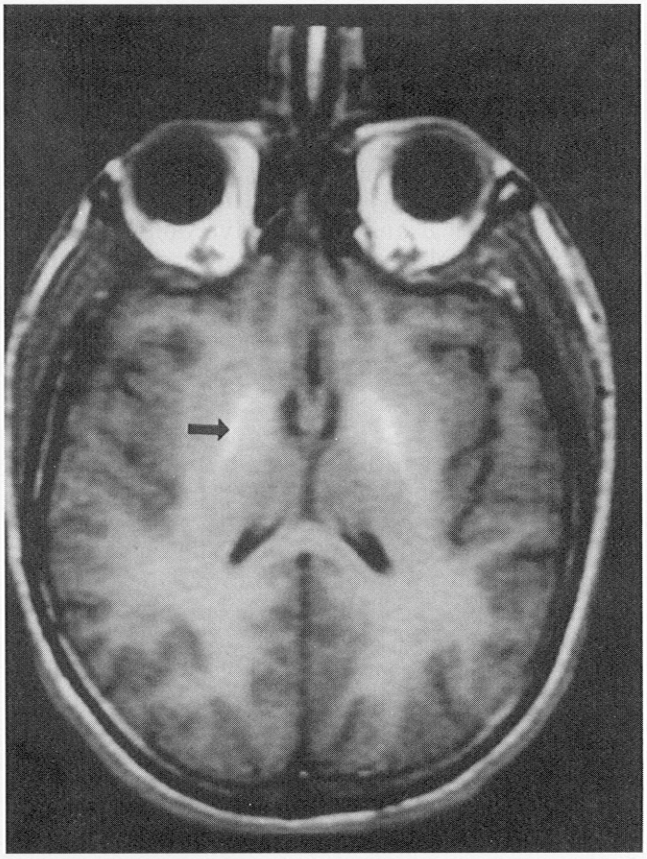

Figure 1 Axial T1 weighted MRI showing pallidal hyperintensities (arrow) in a 45-year-old white male with AIDS, chronic active hepatitis B and cognitive dysfunction. A posterior fossa subdural hematoma is present without obstruction or displacement of the fourth ventricle.

Table 1 ^{1}H MRS data from a voxel of tissue in the left temporal region of a neurologically impaired patient co-infected with HIV and HBV

40 ms TE			*270 ms TE*
NAA:CR	CHO:CR	INS:CR	^{1}H GLX:CR
1.43	0.69	0.40	0.75

NAA = N-acetylaspartate; CR = creatine-phosphocreatine; CHO = choline; INS = inositol; GLX = glutamine-glutamate

Table 2 Single voxel ^{1}H MRS data from five HIV-1 seronegative controls without neurological disease

Control	*NAA:CR*	*CHO:CR*	*INS:CR*	*^{1}H GLX:CR*
1	1.53	1.01	0.81	0.44
2	1.68	1.09	0.80	0.42
3	1.64	1.01	0.76	0.41
4	1.56	0.95	0.71	0.29
5	1.65	0.80	0.73	0.41
Mean	1.61	0.97	0.76	0.39
Standard deviation	0.06	0.10	0.04	0.06

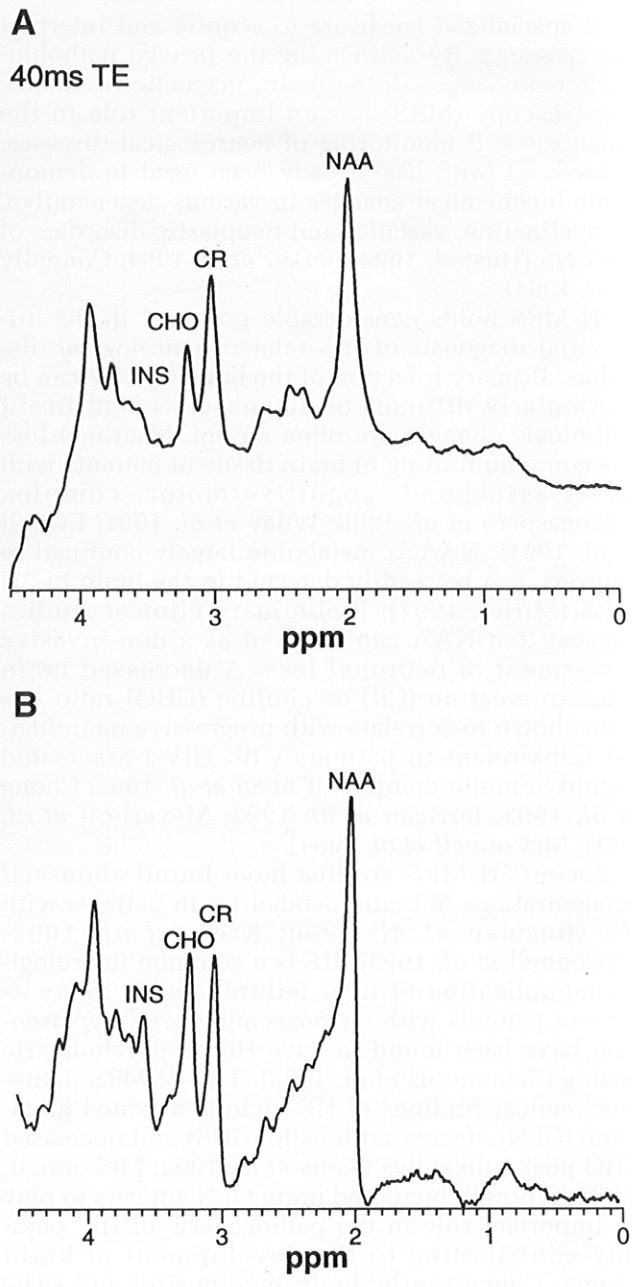

Figure 2 (A) *In vivo* single voxel ^{1}H MRS (40 ms TE) showing NAA, CR, CHO and INS peaks. The CHO:CR, INS:CR and NAA:CR ratios are decreased compared to controls. (B) Single voxel ^{1}H MRS of a normal volunteer (40 ms TE) is shown.

status, a repeat MRI was performed. The brain MRI again showed only a small subdural hematoma, unchanged from the previous examination. Pallidal T1 hyperintensities were also observed (Figure 1). These changes were insufficient to explain the marked cognitive dysfunction.

^{1}H MRS was then performed and showed a marked increase in glutamine-glutamate (GLX) with respect to the creatine-phosphocreatine peak (CR) (α^{1}H GLX:CR). A decrease in choline:creatine-phos-

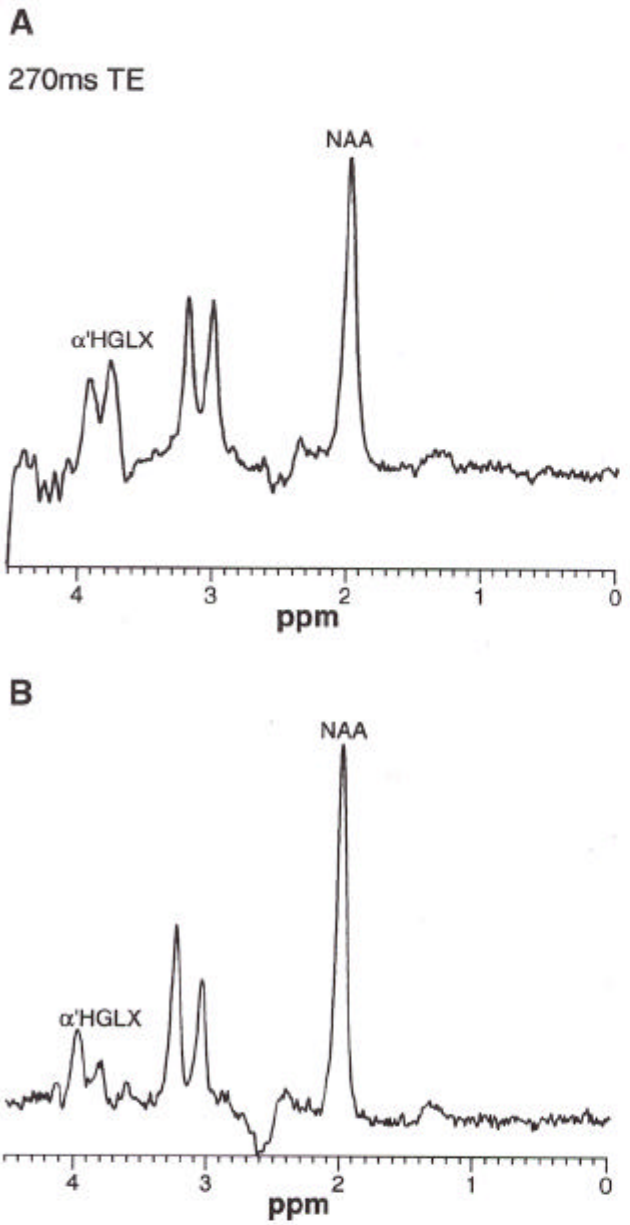

Figure 3 (A) *In vivo* single voxel ^{1}H MRS (270 ms TE) showing α'HGLX peak at 3.75 ppm. The α'HGLX:CR ratio is increased compared to controls. (B) Single voxel ^{1}H MRS of a normal volunteer (270 ms TE) is shown.

phocreatine (CHO:CR) and myoinositol:creatine-phosphocreatine (INS:CR) ratios was also observed (Table 1, Figures 2, 3). The CR peak represents both creatine and phosphocreatine resonances. Creatine-phosphocreatine (CR) is present through the brain and was used as the internal reference signal for peak intensity ratios. Normal control values from uninfected volunteers are shown in Table 2.

Decrease in the ratio of NAA to CR or CHO appears to be a surrogate marker for HIV-1-associated cognitive/motor complex. A significant decrease in NAA was not observed in this case. Therefore,

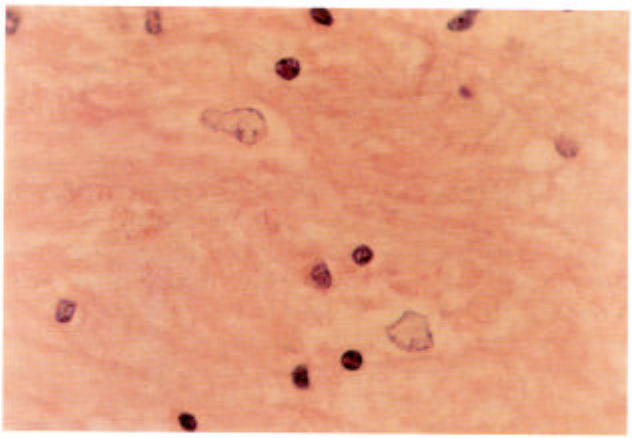

Figure 4 Histopathological examination of brain tissue of a patient who died of chronic active hepatitis B and HIV-1 disease. Microscopic examination reveals paucity of abnormalities with only Alzheimer type II astrocytes in the globus pallidus (× 700).

the spectral findings in this patient were consistent with HE not the HIV-1-associated cognitive/motor complex. Despite treatment of HE with lactulose and general supportive measures the patient gradually became unresponsive and died 8 days after admission. An autopsy was performed. Post-mortem evaluation of the brain revealed a small subdural hematoma with subarachnoid hemorrhage, small areas of focal acute neuronal degeneration, Alzheimer type II astrocytosis, and scattered perivascular macrophages with hemosiderin (Figure 4). There were no microglial nodules, multinucleated giant cells, or inflammation. The liver was small (750 g) with mixed macronodular and microondular cirrhosis. Immunoperoxidase stains for hepatitis B surface and core antigens were negative. These findings, *in toto*, confirmed the diagnosis of HE and the conclusions reached by ^{1}H MRS.

Discussion

Chronic active hepatitis complicates the management of HIV infection, and *vice versa*. When neurological complications develop in an HIV-infected patient co-infected with HBV, diagnosis can be difficult. In the absence of tests that can differentiate HIV and HBV-related neurological syndromes, ^{1}H MRS proved clinically helpful.

Pathogenetic mechanisms in HIV-1-associated cognitive/motor complex and HE are quite different. Productive HIV infection in the brain appears to be confined to macrophages, microglia and multinucleated cells (Lipton and Gendelman, 1995). Pathological abnormalities in HIV-encephalitis are heterogeneous and include gliosis, white matter pallor, multinucleated giant cells and vacuolar myelopathy. While neurons are not directly infected by HIV, neuronal loss is a hallmark feature.

Mechanisms for neuronal loss remain poorly understood, but likely represent damage by soluble products secreted by macrophages.

Inimically, the neuropathogenesis of HE does not represent infection of the brain by HBV. HE is likely attributable to toxic substances derived from metabolic pathways that bypass the liver through anatomical or functional shunts. Several compounds have been implicated including ammonia and mercaptans (King, 1993; Mousseau and Butterworth, 1994). Biogenic amines and other enteric products may also be responsible. Chronic exposure of brain to toxic levels of such compounds likely alters glutamatergic and serotoninergic neurotransmitter systems, causing failure of neurotransmission. Specific neurotransmitter systems implicated in the pathogenesis of HE include the excitatory amino acid glutamate, as well as neuroactive biogenic amine metabolites. Moreover, a subgroup of patients with HE have increased blood and CSF concentrations of substances that bind to gamma-aminobutyric acid (GABA)-related receptors. Pathological changes are usually confined to hyperplasia of astrocytes and do not include neuronal damage.

Despite diverse pathologies, the clinical manifestations of HIV-1-associated cognitive/motor complex and HE are similar. Both present with cognitive, motor and behavioral abnormalities. Symptoms typically start with difficulty concentrating and forgetfulness. Psychomotor slowing may be evident in early HIV-1-associated cognitive/motor complex, but symptoms of motor dysfunction such as clumsiness and unsteady gait often lag behind intellectual deficit. Patients with HE may exhibit tremor, slurred speech, dyskinesia and ataxic gait.

In the absence of diagnostic tests for either syndrome, the evaluation of neurological impairment consists of exclusion of other treatable causes of dementia. CSF examination is often unremarkable with the possible exception of mild protein elevation. Neuropsychological testing may show abnormalities in both syndromes; in particular those measuring attention, concentration and motor performance. Though the differences may be subtle, performance time under pressure, motor speed, and alternation between two performance rules or stimulus sets are generally the tests most sensitive to HIV-1-associated cognitive/motor complex (Bornstein *et al*, 1991) whereas patients with liver cirrhosis primarily exhibit disturbances in tests such as number connection and line tracing (Elsass *et al*, 1978). However, neuropsychological testing alone is likely to have a high rate of misclassification in HIV-1-associated cognitive/motor complex and appears to be more effective when used in conjunction with neurological evaluation. The former is useful in quantifying treatment effects by measuring levels of performance, and the latter more useful in classifying patients by establishing diagnosis and function status (Sidtis *et al*, 1993). In HE, blood ammonia levels are usually elevated but correlate poorly with clinical status (Mousseau and Butterworth, 1994). There is no correlation with liver function tests. Brain MRI is not particularly helpful to patients with HE, though may identify structural problems, such as subdural hematomas. MRI may also show pallidal T1 hyperintensities consistent with chronic liver failure, but these changes do not correlate with the severity of progression of hepatic encephalopathy (Kulisevsky *et al*, 1982). With advanced HIV-1-associated cognitive/motor complex, CT or MRI scans may show cortical atrophy, but are insensitive to subtle changes associated with neuronal loss (Donovan Post *et al*, 1991; Dooneief *et al*, 1992). When gliosis and neuronal loss coexist, morphological changes may not be observed on neuroimaging (Menon *et al*, 1990). Both HIV-1-associated cognitive/motor complex and HE remain diagnoses of exclusion.

Recent investigations have demonstrated that ^{1}H MRS can detect neuronal loss in HIV-infected individuals with cognitive dysfunction (Cohen *et al*, 1992; Jerrigan *et al*, 1993; Meyerhoff *et al*, 1993). A decrease in the NAA:CR ratio has been observed in patients with AIDS compared to HIV-seropositive individuals. Moreover, HIV-seropositive patients with cognitive and motor dysfunction showed significantly lower brain NAA levels than neurologically intact individuals. A decrease in NAA:CR ratio over time has been observed in HIV-infected individuals with and without neurological impairment (McConnell *et al*, 1994). The NAA:CR ratio was decreased in our patient suggesting mild neuronal loss, but the reduction was insufficient to explain the severe progressive encephalopathy.

The striking spectral findings in our patient were decreased CHO:CR and INS:CR, and increased α^{1}H GLX:CR ratios (Figures 2, 3). These findings are consistent with the pathobiochemical changes of HE. The elevated α^{1}H GLX is consistent with an increase in brain glutamine, known to develop in liver failure (Mousseau and Butterworth 1994). The ^{1}H MRS findings in this case were, thus, consistent with HE and not with HIV-1-associated cognitive/motor complex.

This report suggests that *in vivo* ^{1}H MRS may be useful in differentiating HIV-1-associated cognitive/motor complex from HE. The ^{1}H MRS findings were confirmed by pathologic changes seen at autopsy, which were consistent with a metabolic encephalopathy. Alzheimer type II astrocytes, cells characteristic of HE, were seen in the globus pallidus. Although the features of HIV encephalitis do not necessarily correlate with the degree of HIV-1-associated cognitive/motor complex, no such features of HIV encephalitis were identified.

^{1}H MRS can be performed using clinical MR images, available in most hospitals. The test is rapid (15–30 min) and non-invasive. In cases of neurolog-

ical impairment without morphological changes in the brain or diagnostic findings in CSF, ^{1}H MRS may prove a useful adjunctive tool or surrogate marker. Permitting earlier diagnosis, ^{1}H MRS may expedite management and guide clinical decisions. Sequential studies may facilitate monitoring of disease progression and response to therapy. Thus ^{1}H MRS may ultimately play an important role in diagnosis and management of HIV-related neurological impairment.

Materials and methods

Proton magnetic resonance spectroscopy (^{1}H MRS) examination was done using a clinical MR imager (Signa, GE Medical Systems, Milwaukee, WI) operating at a field strength of 1.5 Tesla. A preliminary T1 weighted axial brain MRI was used for selection of a volume of tissue (Voxel size $3 \times 3 \times 3$ cm) in the left temporal region (grey/white matter). The PRESS sequence was used with a repetition time (TR) of 2000 ms and echo times (TE) of 40 ms and 270 ms. The spectral width was 2000 Hz. The prominent NAA peak was assigned 2.0 ppm and was used as an internal reference for all spectra. Ratio measurements are given as relative peak intensities of NAA, CHO, INS, and GLX with respect to the CR peak. The NAA:CR, and CHO:CR, and the INS:CR ratios were determined on spectra at 40 ms TE. The α^1H GLX:CR ratios were measured from the α^1H peak at 3.75 ppm on 270 ms TE spectra.

The spectral data were processed on a SUN-SPARC II workstation using a SA/GE software (GE Medical Systems). Spectral processing included exponential multiplication line broadening of 1 Hz, zero filling to 8K and 1-D Fourier transform. The spectra, pulse sequences and processing were done in the same fashion for the patient and the controls.

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