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Proton MR Spectroscopy of Brain Abnormalities in Neonates Born to HIV-Positive Mothers

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PURPOSE: To examine the sensitivity of proton MR spectroscopy for detecting early central nervous system abnormalities in neonates born to human immunodeficiency virus (HIV)–positive mothers. **METHODS:** Asleep, unsedated, and continuously monitored by electrocardiography, 10 newborns, 5 with HIV-positive and 5 with HIV-negative mothers, were studied within the first 10 days of life in a 1.5-T scanner. After T1- and T2-weighted images were obtained, proton spectra were performed using voxels of interest (3.4 cm^3) in the deep parietooccipital white matter. Peaks were identified as N-acetyl-aspartate (2.0 ppm), creatine and phosphocreatine (3.0 ppm), choline (3.2 ppm), and inositol (3.5 ppm). Peak areas were used to calculate metabolic ratios: N-acetyl-aspartate to creatine, inositol to creatine, and creatine to choline. **RESULTS:** All newborns of HIV-positive mothers had abnormal proton spectra compared with control infants; a nonspecific amino acid peak in the 2.1- to 2.6-ppm area was elevated, broad, and overlapping the N-acetyl-aspartate peak in all the HIV-exposed newborns and in only 1 of the 5 control newborns. The choline-to-creatine ratio was higher in HIV-exposed newborns at 2.3 ± 0.4 (normal term, 0.9 ± 0.3), as was the N-acetyl-aspartate-to-creatine ratio at 2.6 ± 0.9 (for control subjects, 1.2 ± 0.4). MR images from these brain regions were all considered normal. Because acquired immunodeficiency syndrome develops in only a small fraction of neonates born to HIV-seropositive mothers, the above spectral abnormalities found in all our subjects may result from indirect effects of HIV, such as intrauterine growth retardation. **CONCLUSIONS:** These findings indicate that proton MR spectroscopy might play an important role in detecting early central nervous system complications in newborns of HIV-seropositive mothers.

Index terms: Acquired immunodeficiency syndrome (AIDS); Brain, magnetic resonance; Brain, metabolism; Infants, newborn; Magnetic resonance, in infants and children; Magnetic resonance, spectroscopy

Central nervous system abnormalities are an early and common manifestation of human immunodeficiency virus (HIV) infection, either as a direct effect or as a result of secondary infection or malignancy (1–4). The magnetic resonance (MR) appearance of central nervous system disease in HIV-infected patients has been well described (5, 6). However, MR images are usually normal during the early stages of HIV infection, even though patients may have either clinical or psychometric evidence of central nervous system involvement (5, 7). Recent investigations indicate that MR spectroscopy may be sensitive to central nervous system abnormalities in HIV-infected adults (6–9).

Of infants born to HIV-seropositive mothers, the percentage of those who will become infected with the virus varies from 25% to 40%, according to different authors. Unfortunately, determining which exposed infants are actually infected remains difficult (10, 11). Most assays, including polymerase chain reaction, in vitro antibody production, and HIV-specific IgA and

Clinical characteristics of studied newborns

Patient	Gestational Age, wk	Apgar Scores, 1/5 min	Weight, g	Head Circumference, cm		Perinatal History	Drug Use
Control 1	40	. . .	2720	. . .		Home delivery, hypoglycemia, hypothermia	Cocaine
Control 2	39	8/9	3900	34.5		Fetal alcoholism	Cocaine
Control 3	39	. . .	3530	34.5		Rule out sepsis	. . .
Control 4	40	8/9	3580	32	(−2 SD)	. . .	. . .
Control 5	40	7/8	3010	31	(−3 SD)	Meconium aspiration, congenital heart disease	Cocaine
HIV 6	42	. . .	2920 (−1 SD)	33	(−2 SD)	Home delivery, right occipital infarct, thrombosis of longitudinal sinus	Cocaine
HIV 7	39	2/6	2780 (−1 SD)	36	(+1 SD)	Hepatitis B, von Willebrand	Cocaine
HIV 8	38	8/9	2650 (−1 SD)	30	(−4 SD)	Syphilis, group B streptococcus	Cocaine
HIV 9	37	8/9	2790	29	(−4 SD)	. . .	. . .
HIV 10	39	9/9	3560	33.5	(−2 SD)	Syphilis, extraaxial hemorrhage along right hemisphere	. . .

virus culture, have fairly high sensitivities (75% to 100%) by 6 months of age (10, 11). Neonatal diagnosis, however, remains a problem, because both polymerase chain reaction and viral culture detect only about 50% of infected infants during this time period. Early diagnosis remains an important goal, because survival of children with perinatally acquired HIV seems to improve with prevention of opportunistic infections, and because treatment of HIV with antiretroviral agents is developing (11). The purpose of the present study is to determine using MR imaging combined with MR spectroscopy whether early central nervous system abnormalities are present in neonates born to HIV-infected mothers.

Materials and Methods

After obtaining informed consent from parents, we enrolled 12 term newborns in the study during a 12-month period (May 1991 to May 1992). Seven infants were born to HIV-seropositive mothers and were the HIV-exposed group. Five were not exposed to HIV during gestation and served as control subjects. Clinical justification for MR spectroscopy included reasons such as home delivery with hypoglycemia and hypothermia or perinatal asphyxia, risk factors for brain injury (see Table). All subjects were studied within the first 10 days of life. The protocol of the study was approved by the institutional review board of the Hospital of the University of Pennsylvania. Studies were performed on a clinical scanner at 1.5 T using a custom-designed double-tuned bird cage–type volume coil, allowing studies of subjects weighing 1000 to 4000 g. Subjects were scanned in the postprandial state, asleep and not

sedated, carefully swaddled on heating pads. They were placed in either the prone or supine position and monitored throughout the procedure with either electrocardiogram or peripheral pulse oximetry and by direct observation by a physician. Standard spin-echo images of the brain (sagittal 600/16/1 [repetition time/echo time/excitations], followed by axial 3500/18/4, 90° flip angle) were obtained initially. Then, localized solvent-suppressed proton spectroscopy was performed. The volume of interest was based on selected axial images. The same technique was used for all subjects regardless of their diagnosis; voxels were located in the parietooccipital white matter and measured 1.5 cm on a side for a total volume of 3.4 cm^3 (Fig 1). This volume was selected to allow accurate location while still maintaining an adequate signal-to-noise ratio without prolonged study time. Attempts were made to obtain bilateral voxels in all subjects but were not always successful. Proton spectra were acquired using the stimulated-echo acquisition method for location with water suppression using three chemical shift-selective radio frequency pulses, each followed by a dephasing gradient. The sequence parameters included the following: 2000/19, mixing time (TM) 10.6, 2Hz-line broadening, zero filling to 2 κ points, and 256 averages.

Analysis of the Data

Images were read blind by two senior neuroradiologists from the American Society of Neuroradiology. Spectroscopic data were analyzed quantitatively by two independent spectroscopists. Two spectra in the HIV-exposed group were excluded from further analysis because of poor quality.

The following peaks were assigned (7, 12–15): N-acetyl-aspartate, 2 ppm; a combined creatine and phosphocreatine peak, 3 ppm; choline, 3.2 ppm; and inositol,

Fig 1. Axial (2700/120) conventional spin-echo image of an HIV-exposed term (39 weeks) 3-day-old newborn (patient 2). The *box* shows the area chosen for proton spectroscopy. Hyperintensity of white matter at this age in this region of the brain is normal.
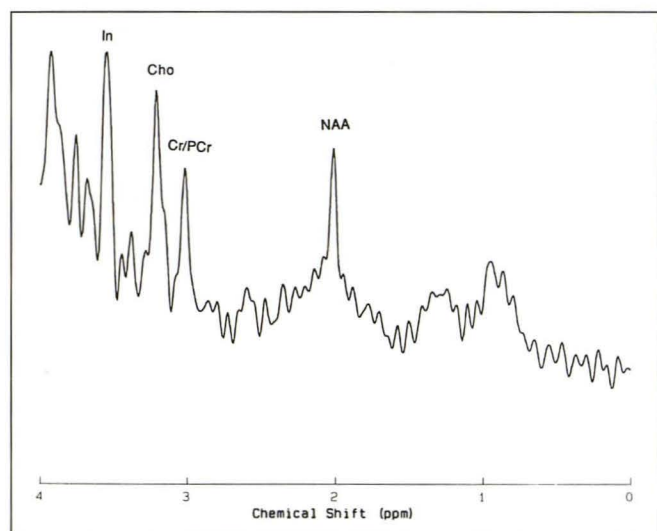

Fig 2. Normal proton spectrum from a control term infant (patient 3). *NAA* indicates *N*-acetyl-aspartate; *Cr/PCr*, creatine and phosphocreatine; *Cho*, choline; and *In*, inositol.

3.6 ppm (Fig 2). Peaks to the right of *N*-acetyl-aspartate included out-of-voxel lipids and lactate when present. The region between 2.1 and 2.6 ppm contains a conglomerate of resonance peaks that cannot be resolved at 1.5 T. Amino acids such as glutamate, glutamine, and γ-aminobutyric acid resonate in this region. We called this the *marker peak* region (7).

Peak area ratios were calculated. The results of the HIV-exposed group were compared with spectroscopic data obtained from control subjects. In addition to quantitative analysis, visual qualitative evaluation of the spectra was performed by a blinded, experienced spectroscopist who rated the studies as normal or abnormal.

Statistical analysis was done using an unpaired t test. Values of $P < .05$ were considered significant.

Results

Results reported here concern the five HIV-exposed newborns whose spectra could be interpreted and the five control newborns. Bilateral voxel analysis was obtained in four of the five control newborns and in three of the five HIV-exposed newborns. Spectra, when obtained bilaterally, were comparable from side to side within the same newborn.

Clinical characteristics and history for each newborn are presented in the Table. There are no significant differences in gestational age or Apgar scores between the two groups. Signs of intrauterine growth retardation were found in four of the five HIV-exposed newborns, as evidenced by reduced head circumference of -2 SD or more, present in only two of the five in the control group.

Three of the five mothers in the control group and three of the five mothers in the HIV-exposed group had used cocaine. HIV seropositivity was attributed to heterosexual transmission in three of the five mothers. Because all the mothers denied any history of intravenous drug use, the origin of HIV seropositivity in the other two mothers remains unclear. None of the HIV-positive mothers received any treatment during pregnancy.

For all of the newborns, except two in the HIV-exposed group, the MR images were considered normal (Fig 3), especially with regard to the volume selected for MR spectroscopy. One newborn had a right occipital infarct with a thrombosis of the sagittal sinus. Another had a small subdural hematoma along the lateral aspect of the right hemisphere. None of these abnormalities overlapped with the voxel used for the spectra acquisition. All newborns had bilateral spectral acquisition except one in the HIV-exposed group and one in the control group. Metabolite ratios calculated from the left hemisphere in this newborn were consistent with those obtained in the newborns exposed to HIV but with normal imaging findings.

In a blinded qualitative assessment, our spectroscopists were able to categorize spectra as
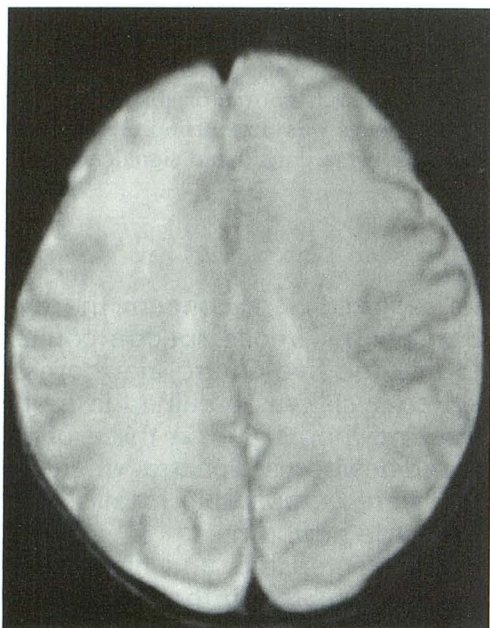
Fig 3. Axial (4000/126) fast spin-echo image of an HIV-exposed newborn (patient 7). The posterior parietal white matter demonstrates normal hyperintensity in newborns.
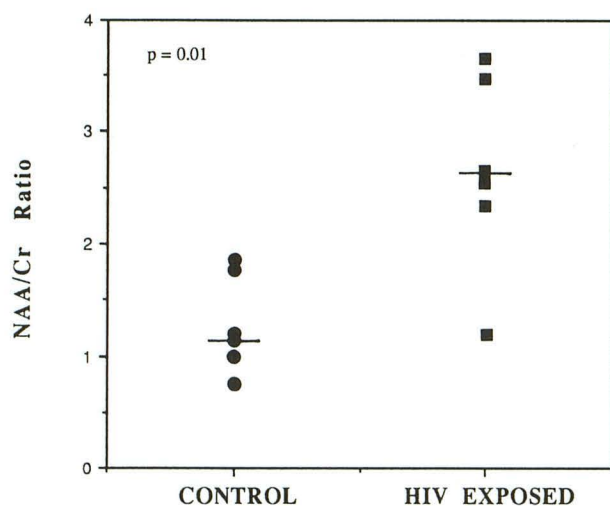

Fig 4. Comparison of N-acetyl-aspartate-to-creatine (NAA/Cr) ratios in control and HIV-exposed subjects. (Each observation in each group represents the value obtained for one newborn.)
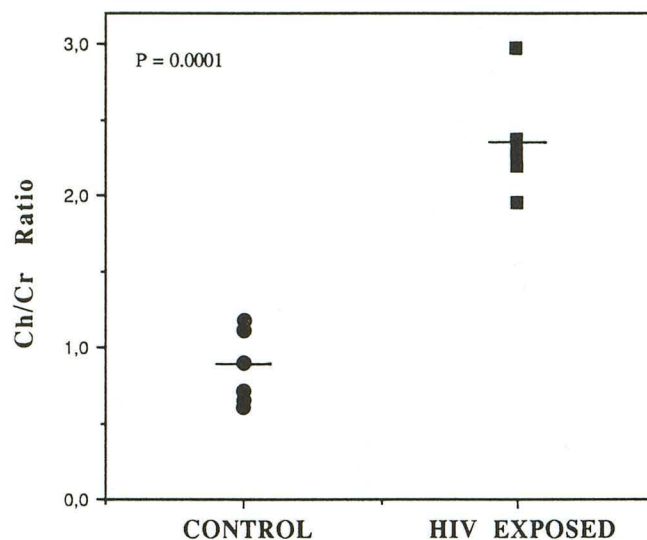

Fig 5. Comparison of choline-to-creatine (Ch/Cr) ratios in control and HIV-exposed subjects. (Each observation in each group represents the value obtained for one newborn.)

abnormal in four and possibly abnormal in one of the newborns in the HIV-exposed groups. In the control group, two of five were thought abnormal.

Figure 4 shows the comparison of N-acetyl-aspartate-to-creatine ratios between the control group on the left and the HIV-exposed group on the right. The N-acetyl-aspartate-to-creatine ratio is significantly ($P = .01$) higher in the HIV-exposed group (2.6 ± 0.9) than the control group (1.2 ± 0.4). Figure 5 shows the comparison between choline-to-creatine ratios in the control group on the left and the HIV-exposed group on the right. The choline-to-creatine ratio is significantly ($P = .0001$) higher in the HIV-exposed group (2.3 ± 0.4) than in the control group (0.9 ± 0.3). With our small sample size, we were not able to demonstrate a significant difference between HIV-exposed and control newborns for the N-acetyl-aspartate-to-choline ratios (mean, 1.1 ± 0.5 in the HIV-exposed group versus 1.6 ± 0.7 in the control group), but there was a trend for this ratio to be smaller in the HIV-exposed group. The inositol-to-choline ratio was not significantly different between the two groups (mean, 1.4 ± 0.2 versus 2.1 ± 1).

The blinded reading by two independent spectroscopists showed the presence of a conglomeration of peaks located between 2.1 and 2.6 ppm, the marker region, in four of the five HIV-exposed newborns and in only one of the five control newborns (Fig 6). To evaluate this marker region, we calculated a marker ratio. The marker ratio was defined as the ratio of the amino acid peak over the creatine peak. This ratio was calculated to take into account this amino acid peak but not in its absolute value. The origin of this amino acid peak remains unclear but may indicate a release of excitatory amino acids, such as glutamate. The presence of a marker-region peak was verified by having the spectra processed blind by two spectrosco-
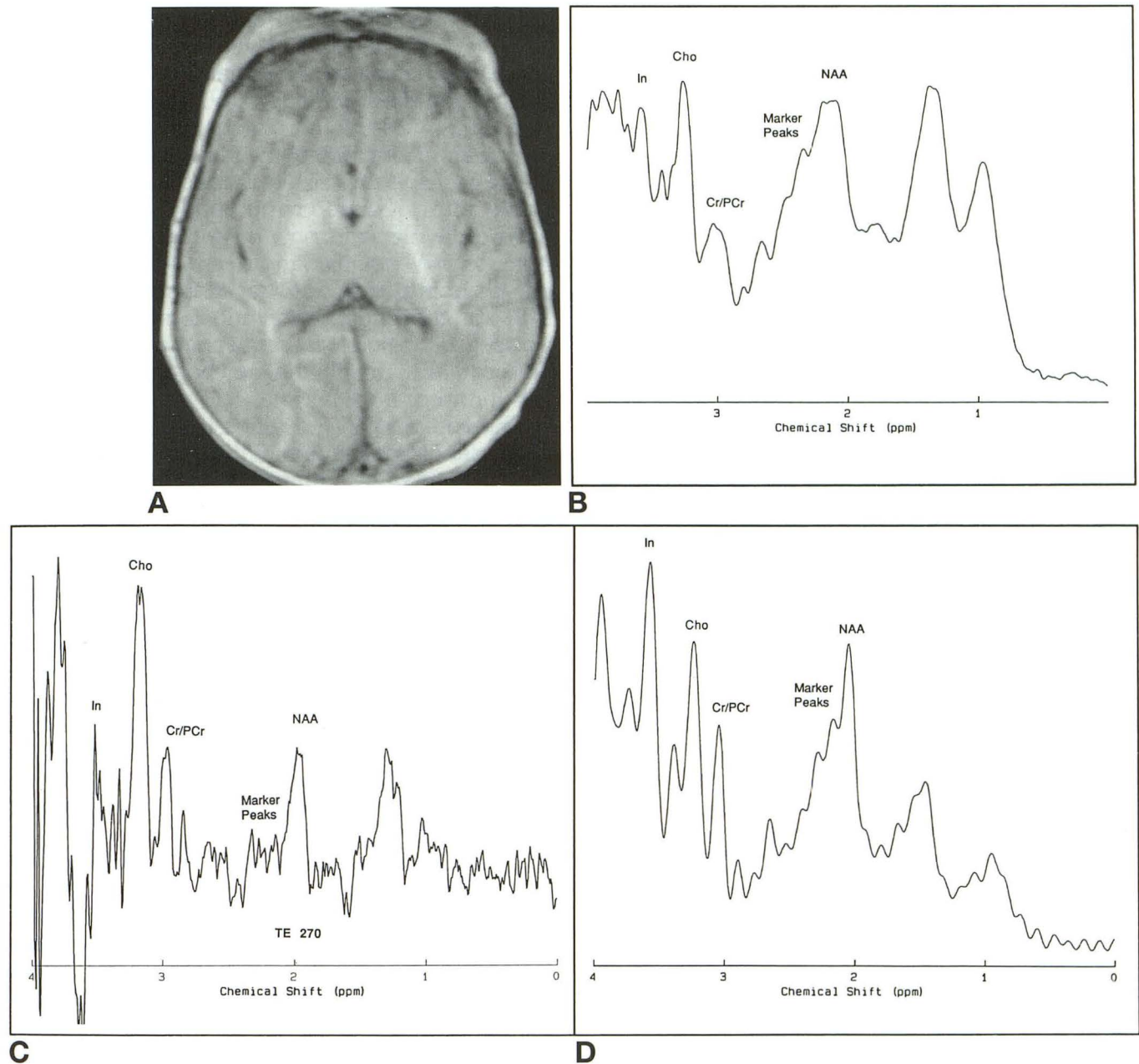
Fig 6. *A*, Axial (500/12) image of an HIV-exposed term 2-day-old newborn (patient 8). The posterior limb of the internal capsule is hyperintense, reflecting normal myelination.

B, Proton spectrum from the same HIV-exposed newborn using a short echo time (16 milliseconds). Note the relative decrease in *N*-acetyl-aspartate (*NAA*), increase in choline (*Cho*), and decrease in creatine and phosphocreatine (*Cr/PCr*) compared with a spectrum from a control term newborn. Also note the broad increase between 2.1 and 2.6 ppm, representing marker peaks.

C, Proton spectrum of same newborn (same examination, same voxel as in *B*) using a longer echo time (*TE*, 270 milliseconds). Note the decrease of marker-region peaks.

D, Proton spectrum from the contralateral side in the same newborn using a short echo time. Changes are similar to those in *B*.

pists. The marker-region peak was considered present only if found in both analyses. It was significantly higher ($P = .005$) in the HIV-exposed group (2.4 ± 0.8) than the control group (0.7 ± 0.2).

To test if the spectra in HIV-exposed newborns were different than in the control subjects, we calculated an aggregate score by adding *N*-acetyl-aspartate-to-choline + *N*-acetyl-aspartate-to-creatine + inositol-to-creatine +

choline-to-creatine. This aggregate score was significantly (P = .002) higher in the HIV-exposed group (8.8 ± 1.3) than the control group (5 ± 1.2).

Discussion

Our data indicate that brain proton spectra may be significantly altered, even if MR images appear normal in term neonates born to HIV-infected mothers. N-acetyl-aspartate-to-creatine and inositol-to-creatine ratios are significantly higher, and the creatine-to-choline ratio is significantly lower in the brains of neonates born to HIV-positive mothers. Furthermore, a broad marker peak consisting of a conglomeration of amino acids between 2.1 and 2.6 ppm was found more frequently in HIV-exposed newborns. At echo times of 270, the intensities of these peaks are markedly reduced because of J modulation and short apparent T2s.

Values of metabolite ratios obtained in our term control neonates are comparable to values of healthy neonates reported in the literature (14, 15). The inositol-to-choline ratio is not significantly altered in the HIV-exposed group. Although we could not demonstrate a statistically significant change in N-acetyl-aspartate to choline in our small sample, there was a trend for this ratio to be lower in the exposed group. The greatest alterations are a decrease in creatine and phosphocreatine relative to N-acetyl-aspartate and inositol. It is striking that the modified metabolite ratios have a standard deviation as small as that for the control subjects but around a different mean value.

The differences observed in proton spectra in HIV-exposed newborns can be compared to the changes observed in spectra in HIV-positive adults. One study reports that two patients with clinical and/or psychometric evidence of central nervous system involvement had marked reductions of N-acetyl-aspartate-to-creatine and N-acetyl-aspartate-to-choline ratios (3). This finding supported the hypothesis that neuronal loss is present in regions appearing normal on MR (5, 7, 9). In another recent study (7) of 10 HIV-1-seropositive patients with a wide range of clinical findings, the N-acetyl-aspartate-to-creatine ratio was consistently lower and the choline-to-creatine ratio consistently higher than age-matched control subjects. The decrease in N-acetyl-aspartate is thought to be secondary to neuronal injury and/or neuronal loss, because N-acetyl-aspartate is found in only neurons and not in glial cells (16, 17). It remains unclear whether neuronal injury is a direct or indirect effect of HIV. In the newborns exposed in utero to HIV in our study, brain proton spectra did not show definite changes in N-acetyl-aspartate. This is reasonable considering that acquired immunodeficiency syndrome develops in only a fraction of persons born to HIV-positive mothers, with predictive values going from 25% for the most recent to 50% for the earliest and most pessimistic reports (10, 11). However, spectra show other abnormalities in all the newborns exposed to HIV in utero.

The fact that all the ratios including creatine as a denominator are higher in HIV-exposed newborns suggests that their creatine levels are lower than in control newborns. This could not be verified because no use was made of an external reference. Even if the decrease in creatine could not be excluded, its relevance and its link to creatine kinase equilibrium changes are not well known. The large peaks of amino acids found in all HIV-exposed newborns suggest the presence of more amino acids, such as glutamate, aspartate, and γ-aminobutyric acid, in the brains of HIV-exposed newborns. This could be related to a release of excitatory amino acids or an inflammatory process in response to the presence of HIV in the central nervous system, but it presupposes that HIV was already present in the brain.

Even if the alterations observed may be attributed to HIV exposure in utero, their interpretation remains uncertain, and follow-up data are essential. At the time of this publication, none of the subjects is known to have evidence of infection by the virus. For some of the children it is already clear that they are not infected. Spectra alterations in all the exposed newborns may reflect the presence of HIV, but this presupposes that HIV is already present in the brains of HIV-exposed newborns. Their origin remains unclear, and follow-up spectroscopy would be of interest.

Because of possible contributions by other factors to these spectral changes, we analyzed the pregnancy history, especially with regard to treatment or drug use. None of the mothers received therapy for her HIV infection. All the mothers denied intravenous drug use. Three of five mothers in the control group and three of five in the HIV-exposed group used cocaine dur-

ing their pregnancies. HIV was transmitted heterosexually to three of five mothers. However, cocaine use in reality may be a marker for intravenous drug use, and thus a risk factor for HIV. Retrospective analysis of data to find confounding factors is always difficult. However, to be relevant for such consistent changes in all the spectra, the factor would have to be common to all the newborns; no single factor met such criteria, except perhaps intrauterine growth retardation, which was found in all the HIV-exposed newborn. Although such spectral changes have not yet been reported in growth-retarded newborns, they remain possible confounding factors (18). Intrauterine growth retardation with small head circumference is probably linked to cocaine exposure, considering that this type of drug use was reported.

The results of the present study show the important role that MR spectroscopy may play in early detection of brain involvement in HIV-exposed neonates. Our study suggests that spectroscopy may reveal abnormalities in infants who have normal MR findings. It seems that proton MR spectroscopy holds promise as an early diagnostic modality for central nervous system involvement in perinatally acquired HIV (7, 9, 18). Although these spectral abnormalities were found in all the HIV-exposed newborns, their future HIV status remains uncertain. The changes that we observed may be transient responses of the brain to HIV, may be related to indirect HIV effects on the brain, or simply may be associated with intrauterine growth retardation. A longitudinal study is necessary to answer these questions.

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