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Brain Lactate and *N*-Acetylaspartate in Pediatric AIDS Encephalopathy

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Summary: Two children with acquired immunodeficiency syndrome (AIDS) and progressive encephalopathy underwent MR spectroscopy before and after antiretroviral therapy. Initial MR spectroscopy of the basal ganglia region showed decreased *N*-acetylaspartate (NAA)/creatine (Cr) and a lactate peak. After therapy, there was improvement in NAA/Cr and an absence of the abnormal lactate peak. We suggest that decreased NAA/Cr in AIDS is reversible, that brain lactate might correlate with inflammation, and that MR spectroscopy can be useful in treatment trials.

Prior studies have suggested that proton magnetic resonance (MR) spectroscopy of the striatum is useful in defining acquired immunodeficiency syndrome (AIDS) encephalopathy (1, 2). Children with progressive encephalopathy have lower *N*-acetylaspartate/creatine (NAA/Cr) ratios than do control subjects and children with AIDS both with and without static encephalopathy (2). NAA/Cr reduction is thought to correspond to neuronal changes (1, 2), which in AIDS are caused by infected macrophages and microglia, not by direct neuronal infection (3).

Two children with AIDS had not only reduced NAA/Cr but also lactate peaks. The initial MR spectroscopic findings in these two patients were reported in a previous publication (2). The children were subsequently studied longitudinally, and those findings are reported here. The patients showed neurodevelopmental and MR spectroscopic improvement after antiretroviral therapy.

Patients and Methods

The MR spectroscopic technique, which was performed on a 1.5-T MR unit, was described previously (1, 2). The single-voxel spectra were acquired with the point-resolved spectroscopy (PRESS) technique (1600/136/128 [repetition time/echo time/excitations]); in the event that lactate was present, an additional spectrum was acquired at a longer echo time (288 milliseconds) to better define the lactate peak. An automated single-voxel proton spectroscopic technique (PROBE/SV; GE Medical Systems, Milwaukee, Wisc) was used with a 2.5-kHz spectral width, 2048 sample points, and 128 averages. The peak area ratios of NAA/Cr and choline (Cho)/Cr were obtained from the spectrum with an echo time of 136 milliseconds (1, 2); the peak area ratio of lactate/Cr was measured from the spec-

trum with an echo time of 288 milliseconds for better definition of the lactate peak.

The region of interest was the basal ganglia, including parts of the caudate, globus pallidus, putamen, thalamus, cerebrospinal fluid (CSF), and internal capsule (Fig 1). This region seems to be the most sensitive in childhood AIDS encephalopathy (1, 2), and the location of the voxel was reproduced visually and always obtained by the same investigator. The left frontal white matter, which may show abnormalities in AIDS, was a second region of interest.

Sixty-three children (45 with AIDS and 18 control subjects), age 2 weeks through 17 years, underwent MR spectroscopy as part of a prior study (2). The two with lactate were from a group of seven (age range, 42 weeks to 12 years) with progressive AIDS encephalopathy (defined as a recent [less than 1 year] deterioration in neurodevelopmental scores of at least 1 SD) (2). These two were serially studied and are included in this report. Consent was obtained for all studies.

The lactate found in the two children who are the subjects of this article was not reported in the prior publication, because the potential implication of lactate was not appreciated until follow-up studies were performed (2). All patients with progressive encephalopathy had NAA/Cr ratios of less than 1.17 (ratios were lower than age-adjusted values in control subjects; normal, >1.36 after age 50 weeks) in the basal ganglia region (2). All patients with progressive encephalopathy, except the two studied serially, were on zidovudine at the time the initial MR spectroscopic study was performed. The two in whom serial MR spectroscopic studies were obtained are described here.

Case 1

This 4-year-old boy with AIDS on didanosine regressed. At the time of initial MR spectroscopy, he had no language and could not sit unsupported. Initial MR imaging showed mild to moderate atrophy. Initial MR spectroscopy in the region of the basal ganglia region showed a reduced NAA/Cr of 0.94 (control range, 1.36 to 1.82), a normal Cho/Cr of 1.10 (control range, 0.75 to 1.45), and a lactate peak with lactate/Cr of 0.28 (Fig 2) (all control data are for children older than 50 weeks). The white matter spectrum showed a reduced NAA/Cr of 0.95 (control range, 1.56 to 2.74), a normal Cho/Cr of 1.18 (control range, 0.76 to 1.76), and no lactate peak. He was treated with continuous intravenous zidovudine for 3 weeks and then oral zidovudine. After 4 weeks of therapy, he sat, crawled, knew 10 words, and could follow simple commands. He continued to

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FIG 1. Coronal (A) and axial (B) T2-weighted (5000/95/1) MR images show the region of interest, which includes the basal ganglia structures of the caudate, putamen, and globus pallidus, and also partial volumes of the internal capsule and thalamus with a typical volume of 9 cm³. The CSF is included but represents a small component of the region.

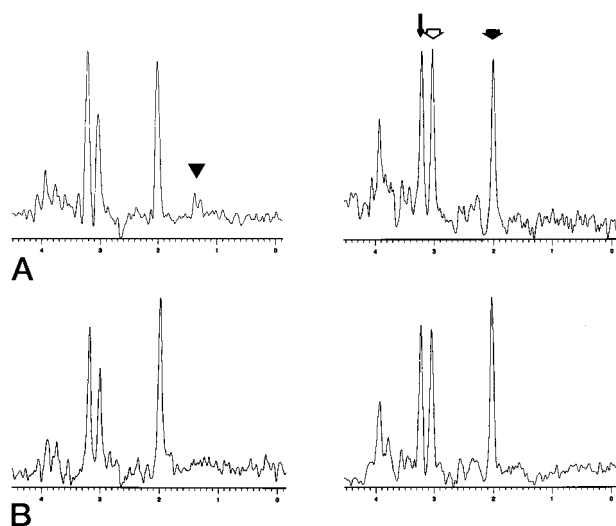
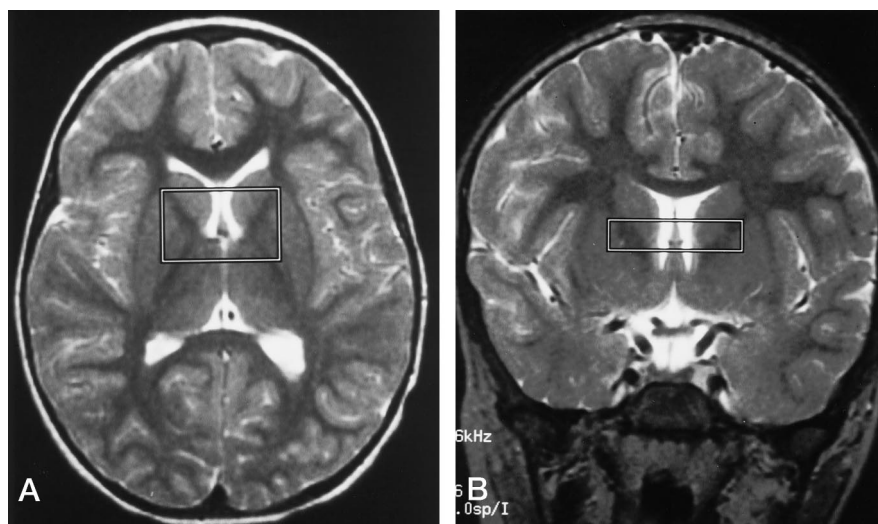


FIG 2. MR spectra from patient 1 obtained with the PRESS technique before (A) and after (B) initiation of antiretroviral therapy. TR was 1600 for all spectra, and TE was 288 for the spectra on the left in A and B (to define lactate peak) and 136 for both spectra on the right (used to calculate NAA/Cr ratio). In A, arrowhead points to the lactate peak, short solid arrow indicates the NAA peak, open arrow the Cr peak, and long arrow the Cho peak. Spectra after therapy show improved NAA/Cr and absence of an obvious lactate peak.

make developmental strides and started to speak in phrases; repeat MR studies 8 months later were unchanged. The spectrum in the striatal region showed an improved NAA/Cr of 1.15 compared with the previous MR spectrum, and no obvious lactate (Fig 2). The Cho/Cr ratio in the basal ganglia region was 1.03. The white matter spectrum was not repeated.

Case 2

This 12-year-old girl with human immunodeficiency virus (HIV) 1 infection had a slowly progressive spastic and cerebellar gait disturbance but remained ambulatory. She deteriorated cognitively as defined by neuropsychological parameters. Initial MR imaging showed atrophy and the possibility of hydrocephalus consequent to aqueductal insufficiency. MR spectroscopy in the basal ganglia region showed a reduced NAA/Cr of 1.05, a normal Cho/Cr of 0.91, and a lactate peak with a lactate/Cr of 0.19. The white matter MR spectrum showed a mildly reduced

NAA/Cr of 1.45, a normal Cho/Cr of 1.11, and no lactate peak. The patient underwent an aqueductal ventriculostomy and was started on oral zidovudine and didanosine. There was no clinical change after ventriculostomy, and a repeat MR study after 1 month was unchanged. The striatal region spectrum showed a further reduction of NAA/Cr to 0.73, Cho/Cr to 0.86, and no lactate peak. Four months later, while continuing on oral zidovudine and didanosine, her gait slowly improved and cognitive function stabilized. Findings on a repeat MR study at 4 months were unchanged, but NAA/Cr improved (basal ganglia, 1.48; white matter, 1.85), with no lactate peak. The Cho/Cr ratios were not significantly changed (basal ganglia, 0.95; white matter, 1.17).

Discussion

Two children who had AIDS with progressive encephalopathy were studied before zidovudine was initiated and again after they were on therapy. The second patient was also studied a third time after therapy was initiated. The two were part of a larger prior cross-sectional study that found reduced NAA/Cr in the basal ganglia region in children with AIDS and progressive encephalopathy (1, 2). Initially, both children had reduced striatal NAA/Cr with a lactate peak, but after starting zidovudine, they improved clinically and had higher NAA/Cr ratios with an absence of the lactate peak.

The rationale for positioning the region of interest within the basal ganglia was that this appears to be the most severely affected region of the brain in children with AIDS and progressive encephalopathy (1, 2). Since NAA is found primarily in neurons (cell body, axon, and synapse) (1, 2, 4, 5), reduced NAA/Cr suggests neuronal dysfunction. In vivo, reduced NAA is found in conditions that injure neurons (eg, metabolic disease, stroke, epilepsy) (4). Apoptotic neurons are found in the striatum of infected brains of children (H. A. Gelbard, L. Sharer, H. James, L. Epstein, "Apoptotic Neurons Are Present in Brains from Children with HIV-1 Encephalitis" (abstract), *Ann Neurol* 1994;36:507), and NAA/Cr reduction resulting from apoptosis is considered to be irreversible. Our two patients showed improved NAA/Cr, temporally related to antiretroviral treatment, as well as clinical improvement or stabilization. We speculate that NAA/Cr improvement may have resulted from neurons that were reversibly damaged, or that it reflected improved synaptic activity.

MR spectra of cerebral lactate peaks are often abnormal. Lactate is found in metabolic disease, infection, ischemia, and hypoxia (6). Our first patient had normal oxygenation (measured by pulse oximetry) and normal findings at MR angiography; our second patient had no clinical evidence of ischemia

or hypoxia and no evidence of an opportunistic infection. In both patients, lactate could have resulted from dysmetabolism of neurons, glial cells, or monocyte elements. Patients with AIDS encephalopathy have active brain inflammation caused by macrophages infected by HIV-1 (7). In vitro MR spectroscopic studies suggest that lactate may result from inflammation rather than from neuronal or astrocytic dysmetabolism (6). We postulate that the lactate in the basal ganglion region may have resulted from the HIV-1 infected inflammatory cells found predominantly in the striatal region of these patients (7, 8). The lack of lactate on follow-up studies suggests the amelioration of inflammation, whereas NAA improvement reflects improved neuronal function. Unfortunately, our study design did not allow us to distinguish brain from CSF lactate, since the region of interest included the ventricles. Because CSF could not be obtained to test for lactate without clinical indications, it is possible that the lactate peaks were from the CSF space. In one study of adult AIDS dementia, the CSF compartment showed a lactate peak at MR spectroscopy (9).

The striatal region inflammation hypothesis, furthermore, may explain the striatal hypermetabolism found with fludeoxyglucose F 18 positron emission tomography in patients with early adult AIDS encephalopathy (10). Patients initially show increased striatal metabolism, with cortical and striatal hypometabolism developing later. The early basal ganglia hypermetabolism may be the result of inflammation. Later, neuronal damage results, producing a diffuse hypometabolism.

In summary, MR spectroscopy shows a reduction in striatal region NAA/Cr in childhood progressive AIDS encephalopathy. This reduced ratio is found primarily in patients in whom cognitive function has deteriorated as compared with those who have a static encephalopathy (2). This reduction, in some patients, is reversible and correlates with clinical stabilization. We speculate that lactate peaks may result from the striatal inflammation found in central nervous system HIV-1 infection (7, 8), although we cannot exclude that lactate is present in the

CSF. Whether lactate also correlates with rapid clinical change remains to be elucidated. A longitudinal trial with central nervous system active antiretroviral agents is planned to define the sensitivity and specificity of proton MR spectroscopy in pediatric AIDS encephalopathy.

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