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[Please Note: This article assumes that registering positive on tests for HIV substitute markers (such as antibodies or generic material associated with the virus) constitutes such a serious health hazard that any serious adverse health consequences that may arise from taking anti-HIV drugs are preferred. As the authors' note, "We should not be daunted in this task by those who think we might be facing a moral dilemma. We are not! We do not have to ask what the trade-offs in quality of life are between the infant who may become HIV infected..and who may then suffer the life-long adverse effects of HIV infection and the HIV-negative infant who might acquire AZT-induced mitochondrial dysfunction and suffer its possible adverse side effects (e.g., muscle, cardiac, and CNS abnormalities)].

Editorial

A New Challenge for the Neuroradiologist: MR Recognition of Mitochondrial Dysfunction in Children Born of HIV-Seropositive Mothers on Antiretroviral Therapy

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In their intriguing article "Cerebral Magnetic Resonance Imaging in Children Born to HIV-Seropositive Mothers and Perinatally Exposed to Zidovudine," Blanche et al (1) raise our awareness about a rare but, in their view, potential complication of zidovudine (3'-azido-2', 3'-dideoxythymidine [AZT]) therapy in this patient population—namely, infant mitochondrial dysfunction. These investigators challenge us as neuroradiologists to be "gatekeepers," asking us to recognize MR imaging abnormalities that might be due to acquired mitochondrial dysfunction in this particular setting. They ask us to include AZT-induced mitochondrial dysfunction in our differential diagnosis of white matter abnormalities, brain stem and gray matter signal intensity changes, and atrophy seen on MR images obtained in infants and children (1). The hope is that with this increased awareness and MR "monitoring" the true incidence of these complications might be recognized and children could then be followed appropriately. In addition, future positive therapeutic options might be advanced as a result of these findings.

Make no mistake, however, the authors are not disputing the unquestioned dramatic and positive impact of AZT therapy on infants in this setting. By no means are the authors advocating discontinuation of this therapy, nor are they saying that their conclusions are positively proved. Acknowledging both the numerous limitations of their retrospective study and the controversy around this hotly debated issue, the authors seek, rather, to raise our consciousness about this important issue and encourage future investigations.

So what facts should the reader know before making a judgment about this article? What has been "scientifically proved" in the past, and what remains to be explored? On the basis of the scientific literature, here is what we do know and what seems noncontroversial. AZT therapy administered orally to mothers 14–38 weeks antepartum,

intrapartum (via intravenous versus oral route) and to the infant orally (4 hours vs. up to 6 weeks) has resulted in a dramatic decrease in HIV transmission to the infant born of an HIV-seropositive mother (2, 3). When combined with caesarian section, the HIV transmission rate has been reduced from approximately 33.3% to <2% (3). One of the first reports of this efficacy of AZT, a nucleoside analog reverse transcriptase inhibitor, appeared in the February 1994 issue of the *New England Journal of Medicine* (2). In that article, Connor et al (2), reporting on the results of the Pediatric AIDS Clinical Trials Group Protocol (PACTG 076), found that the maternal-to-infant transmission of HIV type 1 was significantly reduced (by about two-thirds) with AZT therapy. This was indeed welcome news, because it had previously been reported by Blanche et al in the same journal in 1989 that by 18 months of age about one-third of infants born to HIV-positive mothers would become HIV positive (4). Some of these infants would go on to develop AIDS, and one-fifth of this cohort would die (4). Fortunately, in the study by Connor et al (PACTG 076) no short-term toxic effects were found in mothers and infants treated with AZT (2). Nevertheless, the concern for long-term adverse effects on the developing infant persisted.

Anecdotal data and circumferential evidence bolstered by animal model studies suggested the possibility that AZT could induce mitochondrial dysfunction in the HIV-exposed but uninfected infant (5). In a study by Gerschenson et al, Erythrocebus patas monkeys exposed in utero to AZT resulted in both cardiac and skeletal muscle mitochrondial injury (6). The theory was that AZT became incorporated into both nuclear DNA and mitochondrial DNA (mtDNA), which then caused chain termination, leading to depletion and/or deletions (6). This process was noted to be akin to that seen in genetic mitochondrial disorders in humans, which is observed in 0.01% of the general population as compared with the higher 0.26% 18-month incidence reported in uninfected children exposed to antiretrovirals because of maternal HIV positivity (5). Genetically induced mitochondrial defects are thought to result from a mutation or deletion in mtDNA and cause impaired ATP (adenosine triphosphate) production. Because aerobic metabolism is thereby affected by this mitochondrial damage, a defect in energy metabolism occurs (7). This process has also been noted to share similarities with what is observed in adults with AIDS on long-term AZT therapy—namely, myopathies of skeletal and cardiac muscle, with muscle weakness, wasting, and fatigue and with marked phosphocreatine depletion, which can be observed on spectroscopy (6). Although these effects in adults have been reported to be reversible following cessation of AZT therapy, the fear was that, in the developing fetus and infant, neurobehavioral and other changes due to mitochondrial dysfunction and cellular respiration might not be reversible (6). In 1999 in *Lancet*, a warning concerning the use of antiretroviral nucleoside analogs was made by Blanche et al that mitochondrial toxic effects might develop as a result of the perinatal use of AZT alone combined with lamovudine to prevent mother-to-child HIV transmission (8). In eight HIV-negative children, mitochondrial dysfunction developed months or years after cessation of antiretroviral therapy (8). Documentation of mitochondrial dysfunction was obtained from different tissues by spectophotometry and polarography of respiratory chain complexes (8); however, another study, by Culnane et al, also published in 1999, reached the opposite conclusion (9).

Drawing from the original cohort from the Pediatric AIDS Clinical Trials Group Protocol 076, a new long-term observational protocol was developed, protocol 219 (PACTG 219) (9). Investigators followed 234 uninfected children (born to HIV-infected women enrolled in Protocol 076) every 6 months for 2 years and then prn. One hundred twenty children were identified as being from the AZT group and 112 from the placebo group (9). Monitoring of growth and development, immune status, cognitive function, neoplasm occurrence, and mortality led to the conclusion that there were no adverse effects in those uninfected children exposed to AZT in utero and perinatally (9). Despite the follow-up ranging from 3.2 to 5.6 years, (median 4.2 years), and a subsequent report indicating in the U.S. cohorts no clear evidence for mitochondrial dysfunction in children dying before age 5 (10), caution was advised and longer follow-up was encouraged (9).

In 2003 another red flag was raised in a study comparing the children (n = 30) of HIV-negative mothers to both the children (n = 10) of HIV-positive mothers who had AZT therapy as well as to the children (n = 10) of HIV-positive mothers without AZT therapy (11). Loss of mtDNA and telomere injury was determined by examination of cord blood leukocyte DNA as well as from peripheral blood leukocyte DNA obtained at 1 and 2 years of age (11). Although evidence of mitochondrial dysfunction was in fact found in children of HIV-positive mothers not on AZT therapy, mtDNA abnormalities were nevertheless even greater for those children of HIV-positive mothers who had been treated with AZT (11). A persistent depletion of mtDNA due to AZT focused attention on the need for longer-term assessment of potential delayed toxic effects of AZT on child development (11–13). The concern for functional damage to the exposed child due to interference with CNS circuitry was raised (12). Because differentiation and synapse formation of neurons has been postulated to continue for several years postnatally, the final match up of pre- and postsynaptic neurons was felt to be possibly at risk with such exposure (12). Barret et al echoed these sentiments (5). Drawing from a large French pediatric cohort and from complimentary investigations, 12 children were found in whom the development of neurologic symptoms, abnormal MR imaging findings, and/or a significant hyperlactatemia episode appeared to provide circumstantial evidence for mitochondrial dysfunction in those exposed perinatally to antiretroviral therapy (5).

The current article by Blanche et al in this issue of the *AJNR* addresses these concerns further and examines the potential of MR imaging to capture abnormalities of the CNS that might be caused by AZT-induced mitochondrial dysfunction (1). Retrospectively examining the MR imaging in 49 uninfected children who had been exposed perinatally to antiretrovirals, the authors found MR abnormalities in 16 of 22 children with established or probable mitochondrial dysfunction and eight of the 27 either with unexplained neurologic symptoms or asymptomatic (1). MR abnormalities, (confirmed by two independent rounds of analysis performed by different individuals with good kappa coefficient consensus), were similar to those reported for genetically based mitochondrial dysfunction (7); namely, diffuse T2 hyperintensities in the white matter, T2 hyperintensities in the pontine tegmentum, and (less commonly) atrophy and necrosis in the white matter and basal ganglia involvement (1).

After reading this investigative work, we should ask ourselves whether there are

limitations to this study. The answer is, yes; numerous limitations. Should this deter us from learning from this thought-provoking study or from pushing forward to develop a more controlled and prospective investigation with more rigidly defined MR and clinical criteria? Absolutely not! If anything, this study raises our awareness and challenges us to expand this type of very important investigation. The authors should be congratulated for doing this important initial and original work.

Surely, most this study's limitations can be overcome. Some of those limitations, also acknowledged by the authors, include the lack of a control population; the relatively nonrigorous manner in which the MR images were obtained; the lack of uniformity in MR units and MR pulse sequences; the lack of clear-cut criteria for obtaining both the initial and follow-up images; the difficulty in documentation of "pathologic" white matter T2 hyperintensities in children under 2 years of age, (i.e., the difficulty in gauging myelin maturation in infants); the possible impact of confounding factors on MR findings (such as maternal substance abuse, prematurity, low birth weight, etc); the lack of uniformity in antiretroviral regimens; the differences in geographic origins of the mother and the possible differences in maternal HIV strains; the influence, if any, of HIV-induced mitochondrial dysfunction in the mother of the HIV-negative but AZT-exposed child; and the lack of a prospective study.

Despite these limitations, as neuroradiologists we have an opportunity to help determine whether MR abnormalities can be seen in the HIV-negative infant born to an HIV-positive mother on antiretroviral therapy, and we have an opportunity to determine whether they are reversible, or even preventable.

We should not be daunted in this task by those who think we might be facing a moral dilemma. We are not! We do not have to ask what the trade-offs in quality of life are between the infant who may become HIV infected through placental transmission from an untreated HIV-positive mother and who may then suffer the life-long adverse effects of HIV infection and the HIV-negative infant who might acquire AZT-induced mitochondrial dysfunction and suffer its possible adverse side effects (e.g., muscle, cardiac, and CNS abnormalities). We do not have to engage in a "numbers game;" that is, that there would be a statistically significantly greater number of children adversely affected with HIV if no antiretrovirals were given to the mother as opposed to the very small number of children who might suffer from the potential consequences of AZT-induced mitochondrial dysfunction. This is not the issue at all.

The issue is whether can we learn from these very respected and highly esteemed investigators who have made very important MR observations and who want to explore further all the ramifications of these observations for a very small subset of patients in the hope of further averting the long-term sequelae of these adverse effects. We definitely can learn from this investigation and can further expand on its challenges.

Blanche et al have "opened our eyes" to a new diagnostic possibility when we observe certain MR abnormalities in infants and children. More importantly, they have impelled us to study this issue further. Just think what we could learn from a large multinational

prospective investigation of this particular patient population with rigid clinical and MR criteria, with standardized MR techniques, with the inclusion of control subjects, and with the addition of serial proton MR spectroscopy. The addition of proton MR spectroscopy to the conventional MR workup would be critical to the detection of biochemical abnormalities (such as the presence of lactate) and to the documentation of their reversal or elimination following changes in therapeutic management in this very small subset of HIV-negative infants born to medically treated HIV-positive mothers. The thought of what we could learn from such a prospective study and the potential benefits of this information to patient care are too good to pass up!

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