

Are your **MRI contrast agents** cost-effective?

Learn more about generic **Gadolinium-Based Contrast Agents**.



**FRESENIUS
KABI**

caring for life

AJNR

**Diffusion Tensor Tractography: Exploring
the Cost-Benefit Ratio of Incorporating CSF
Suppression into Fiber Tracing Algorithms**

Christopher D. Lascola

AJNR Am J Neuroradiol 2005, 26 (4) 693-694

<http://www.ajnr.org/content/26/4/693>

This information is current as
of April 18, 2024.

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

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 non-controversial. 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, be-

cause 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 mitochondrial 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 lamivudine 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 differ-

ent tissues by spectrophotometry 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 ad-

versely 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 we can 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!

M. JUDITH DONOVAN POST
Member, Editorial Board

Perinatal Exposure to Antiretroviral Agents: Risks and Benefits

In the United States, approximately 7000 infants are born to HIV-infected women each year. Before 1994, between 20% and 30% of these infants became infected with HIV and developed a chronic HIV infection with a shortened life expectancy. In 1994, results of a multicenter Pediatric AIDS Clinical Trials Group placebo-controlled study of zidovudine given during pregnancy, labor and delivery and to the infant for 6 weeks showed reduction of perinatal transmission of HIV by 67% (1). Following the release of these study results, the U.S. Public Health Service (USPHS) Task Force recommended the use of zidovudine during pregnancy for reduction of perinatal transmission (2). The USPHS Task Force no longer recommends monotherapy as optimal treatment for HIV infection, but continues to include zidovudine as a part of combination antiretroviral therapy given to women during pregnancy both for their own health and for reduction of perinatal transmission (3). This approach has been extremely successful and has reduced perinatal transmission of

References

1. Blanche O, et al. Cerebral magnetic resonance imaging in children born to HIV seropositive mothers and perinatally exposed to zidovudine. *AJNR Am J Neuroradiol* 2004; *this issue*
2. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type I with zidovudine treatment. *N Engl J Med* 1994;331:1173-1118
3. Taylor GP, Low-Beer N. Antiretroviral therapy in pregnancy: a focus on safety. *Drug Saf* 2001;24:683-702
4. Blanche S, Rouzioux C, Moscato ML, et al. A prospective study of infants born to women seropositive for human immunodeficiency virus type I: HIV infection in newborns French collaborative study group. *N Engl J Med* 1989;320:1643-1648
5. Barret B, Tardieu M, Rustin P, et al. Mitochondrial dysfunction in HIV uninfected children. *AIDS* 2003;17:1769-1785
6. Gerschenson M, Erhart SW, Paik CY, et al. Fetal mitochondrial heart and skeletal muscle damage in erythrocytes patas monkeys exposed to in utero to 3'-azido-3'-deoxythymidine. *AIDS Res Hum Retroviruses* 2000;16:635-644
7. Munoz A, Mateos F, Simon R, et al. Mitochondrial diseases in children: neuroradiological and clinical features in 17 patients. *Neuroradiology* 1999;41:920-928
8. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999;354:1084-1089
9. Culnane M, Fowler M, Lee SS, et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women: Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. *JAMA* 1999;281:151-157
10. Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts. *J Acquir Immune Defic Syndr* 2000;25:261-268
11. Shiramizu B, Shikuma KM, Kanemoto L, et al. Placenta and cord blood mitochondrial DNA toxicity in HIV-infected women receiving nucleoside reverse transcriptase inhibitors during pregnancy. *J Acquir Immune Defic Syndr* 2003;32:370-374
12. Mantovani A, Calamandrei G. Delayed developmental effects following prenatal exposure to drugs. *Curr Pharm Des* 2001;7:859-880
13. Poirier MC, Divi RL, Al-Harathi L, et al. Long-term mitochondrial toxicity in HIV- uninfected infants born to HIV-infected mothers. *J Acquir Immune Defic Syndr* 2003;33:175-183

HIV in the United States to between 1% and 4% (4, 5). This decrease in perinatal transmission of HIV has also resulted in a 66% reduction in the number of cases of pediatric AIDS reported in the United States between 1993 and 1997 (6).

In addition, short-course zidovudine alone or in combination with lamivudine has been successful in decreasing perinatal transmission by 40-50% in developing countries (7-9). This success in preventing HIV infection in thousands of infants is, however, also associated with the risk of exposure to drugs with unknown long-term toxic effects. Short-term studies in the United States and Europe of cohorts of infants who were exposed to zidovudine have been reassuring, with no increase in congenital anomalies, cancer incidence, or preterm delivery compared with unexposed controls. There were also no significant differences in immunologic parameters, growth, or neurodevelopment (10-13).

In 1999, however, Blanche et al (14) reported mitochondrial dysfunction in eight of 1754 infants who

had been exposed to nucleoside analogues including zidovudine (ZDV) and lamivudine (3TC) *in utero* or post partum. Two of these infants developed serious neurologic disease and subsequently died. This prompted investigators to look for similar cases in HIV-exposed but uninfected infants. Mitochondrial toxicity in children may be manifested as skeletal muscle and cardiac muscle changes, lactic acidosis, progressive neurologic disease, growth failure and liver, kidney or pancreatic disease (15). The French Perinatal Cohort Study group evaluated 2644 HIV-negative children exposed to antiretrovirals for symptoms compatible with mitochondrial dysfunction. Twelve children were symptomatic: 10/12 had abnormal MR images, 7/12 had an episode of hyperlactemia, and 11/12 had a profound deficit in one of the respiratory chain complexes. This represents an 18-month incidence for neuromitochondrial disease of 0.26% compared with 0.01% in the general population (16). A large retrospective study undertaken by the Perinatal Safety Review Working Group evaluated five large cohorts of infants in the United States comprising more than 20,000 children, half of whom had been exposed to antiretroviral agents: 223 deaths occurring in children less than 60 months of age were reviewed, and evidence for mitochondrial dysfunction as a factor in these deaths could not be established (17). A prospective study of echocardiograms obtained over the first 5 years of life from 382 HIV-negative children born to HIV-infected women did not show evidence for mitochondrial toxicity (18).

There is ample evidence in the literature for mitochondrial dysfunction induced by nucleoside analogues. Although these drugs inhibit the viral reverse transcriptase, they can also inhibit other DNA polymerases, including mtDNA polymerase gamma. Inhibition of this enzyme can result in depletion of the mitochondrial DNA (mtDNA) and mitochondrial dysfunction (19). Gerschenson et al (20, 21) demonstrated fetal mitochondrial heart and skeletal muscle damage in *Erythrocebus patas* monkeys exposed *in utero* to ZDV alone or in combination with 3TC. Poirier et al (22) studied three groups of uninfected infants for markers of mitochondrial toxicity; those born to HIV-negative women ($n = 30$) and those born to HIV infected women ($n = 20$) who either received no antiretroviral therapy ($n = 10$) or zidovudine during pregnancy ($n = 10$). This study demonstrated that zidovudine causes depletion in mtDNA in infants that can persist up to 2 years. Alimenti et al (23) prospectively measured plasma lactate in a group of 38 HIV-negative infants exposed to antiretroviral therapy to investigate the incidence of potential mitochondrial toxicity. Plasma lactate was elevated on at least one determination in 35/38 children followed over the first 6 months of life, with 10 having higher levels (>5 mmol/L). The clinical significance of these findings is uncertain.

In this issue of the *AJNR*, Blanche et al describe a cohort of 49 infants exposed *in utero* and perinatally to antiretroviral agents for reduction of HIV transmission from mother to infant. None of the infants

was infected with HIV. All the infants received treatment with nucleoside reverse transcriptase inhibitors in the postpartum period. Of these, 49 received zidovudine and 34 received zidovudine in addition to lamivudine. Seventeen of these children had exposure to other antiretroviral agents that were not specified. Twenty-two children had evidence for mitochondrial dysfunction, with 18 having neurologic symptoms. Twenty-seven children had no known mitochondrial dysfunction, and of them 14 had neurologic symptoms similar to those found in the group with mitochondrial dysfunction. Seven had persistent biochemical abnormalities by laboratory testing, and six were asymptomatic. MR imaging showed abnormalities of the brain in all but six of the children with mitochondrial abnormalities; in the 27 infants with no mitochondrial dysfunction, eight showed MR imaging abnormalities. It will be important to follow up these children to determine the long-term significance of these MR imaging abnormalities. The findings in this study suggest that some infants exposed to antiretroviral agents including zidovudine and lamivudine may develop mitochondrial toxicity and resultant neurologic or neurodevelopmental abnormalities.

These findings emphasize the importance of both short-term and long-term follow-up for infants exposed to antiretroviral therapy. In the United States, the Pediatric AIDS Clinical Trials Group funded through the National Institutes of Health has established a long-term follow-up protocol that includes both infected and uninfected children exposed to antiretroviral agents *in utero*. These children have been followed up since the opening of this protocol in 1993, and new infants continue to be accrued into this study. After 1994, women were offered monotherapy with zidovudine for reduction of perinatal transmission (2). With the introduction of newer antiretroviral agents, however, drugs acting at different points in the HIV replicative cycle are being used in combination and include nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors. Thus, continued follow-up of infants exposed to antiretroviral agents is imperative.

At present, serious neurologic toxicity has been reported in small numbers of infants exposed to zidovudine or lamivudine. There is an emerging database of information regarding mitochondrial dysfunction in HIV-negative, antiretroviral-exposed infants. There is immediate need for prospective, controlled studies of HIV-exposed infants with the goal of better defining toxicities, including mitochondrial abnormalities, their incidence, and their long-term consequences. If abnormalities occur, are they transient or will they persist, possibly resulting in long-term effects? Elective caesarian section is another technique that reduces the risk of perinatal transmission and is routinely offered to women in the United States whose viral load is greater than 1000 copies/mL at the time of delivery (24, 25). Current recommendations for the treatment of the pregnant woman with HIV infection include combination ther-

apy using at least three drugs (3). Women with low (<1000 RNA copies/mL) or undetectable viral loads in their plasma have a very low risk of perinatal transmission of HIV (26). This raises the question of whether infants born to women with a very low or undetectable viral load need 6 weeks of treatment after delivery for prevention of HIV, or could this course be shortened, thus decreasing exposure to these agents? A combined intervention similar to that used for prevention of hepatitis B infection in neonates whose mothers are infected with hepatitis B by using hyperimmune immunoglobulin along with vaccine at birth may be useful in HIV as well (27, 28). HIV hyperimmune immunoglobulin or monoclonal antibodies directed against HIV proteins given at birth along with an HIV vaccine, once such a vaccine is available, might be an alternative effective strategy. It is imperative that research dollars be available to answer these important questions. We have made significant strides in prevention of perinatal transmission of HIV, but this must be accomplished by using the safest, most efficacious methods available.

It is important to weigh the benefits of antiretroviral therapy against the risk of an adverse event occurring in the woman, the fetus, or the neonate. Worldwide, about 600,000 perinatal HIV infections occur yearly. Use of simple short-course therapeutic regimens in developing countries can prevent between 40–50% of these cases. Dr. Lynne Mofenson of the National Child Institute of Health and Child Development stated in an editorial, “Given the fatal nature of HIV infection, any long-term risk entailed by the *in utero* or neonatal exposure of children to antiretroviral drugs would have to be profound, occur early in life, and occur in a substantial proportion of those exposed to outweigh the proved benefit of antiretroviral prophylaxis in reducing perinatal transmission of HIV”. Current information does not seem to justify changing current recommendations for reduction of perinatal transmission of HIV. Further research to define the spectrum of toxicities and to better understand the mechanism of the mitochondrial effects of these drugs is, however, essential.

GWENDOLYN B. SCOTT

Guest Editor

Department of Pediatrics

University of Miami School of Medicine

Miami, FL

References

- Connor EM, Sperling RS, Gelber R, et al. **Reduction of maternal-infant transmission of human immunodeficiency virus type-1 with zidovudine treatment.** *N Engl J Med* 1994;331:1173–1180
- US Centers for Disease Control. **Public Health Service recommendations on use of zidovudine to reduce perinatal transmission of human immunodeficiency virus.** *MMWR Morb Mortal Wkly Rep* 1994;43:1–20
- Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States, June 23, 2004 [<http://AIDSinfo.nih.gov>]
- Stiehm ER, Lambert J, Mofenson L, et al. **Efficacy of zidovudine and HIV hyperimmune immunoglobulin for reducing perinatal HIV transmission from HIV-infected women with advanced disease: results of Pediatric AIDS Clinical Trials Group Protocol 185.** *J Infect Dis* 1999;179:567–575
- Garcia PM, Kalish LA, Pitt J, et al. **Maternal plasma HIV-1 RNA levels and risk of perinatal transmission.** *N Engl J Med* 1999;341:394–402
- Lindgren ML, Byers RH, Thomas P, et al. **Trends in perinatal transmission of HIV/AIDS in the United States.** *JAMA* 1999;282:531–538
- Shaffer N, Chuachoowong R, Mock PA, et al. **Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomized controlled trial.** *Lancet* 1999;353:773–780
- Guay L, Musoke P, Fleming T, et al. **Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-child transmission of HIV-1 in Kampala, Uganda: HIV-NET 012 randomized trial.** *Lancet* 1999;354:795–802
- Petra Study Team. **Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra Study): a randomized, double blind, placebo controlled trial.** *Lancet* 2002;359:1178–1186
- Culnane M, Fowler M, Lee SS, et al. **Lack of long term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women: Pediatric AIDS Trials Group Protocol 219/076 Teams.** *JAMA* 1999;281:151–157
- Hanson IC, Antonelli TA, Sperling RS, et al. **Lack of tumors in infants with perinatal HIV-1 exposure and fetal/neonatal exposure to zidovudine.** *J Acquir Immune Defic Syndr Hum Retroviral* 1999;20:463–467
- Caselli D, Klersy C, de Martino M, et al. **Human immunodeficiency virus-related cancer in children: incidence and treatment outcome: report of the Italian Register.** *J Clin Oncol* 2000;18:3854–3861
- Tuomala RE, Shapiro DE, Sorenson LM, et al. **Antiretroviral therapy during pregnancy and the risk of an adverse outcome.** *N Engl J Med* 2002;346:1863–1870
- Blanche S, Tradieu M, Rustin P, et al. **Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues.** *Lancet* 1999;354:1084–1089
- Munnich A, Rotig A, Chretien D, et al. **Clinical presentation of mitochondrial disorders in childhood.** *J Inherit Metab Dis* 1996;19:521–527
- Barret B, Tardieu M, Rustin P, et al. **Persistent mitochondrial dysfunction in HIV exposed but uninfected infants: clinical screening in a large prospective cohort.** *AIDS* 2003;17:1769–1785
- Perinatal Safety Review Working Group. **Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts.** *J Acquir Immune Defic Syndr* 2000;25:261–268
- Lipshultz SE, Easley KA, Orav EJ, et al. **Absence of cardiac toxicity of zidovudine in infants: Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study Group.** *N Engl J Med* 2000;343:759–766
- Brinkman K, Ter Hofstede HJ, Burger DM, et al. **Adverse effects on reverse transcriptase inhibitors: mitochondrial toxicity as a common path way.** *AIDS* 1998;12:1735–1744
- Gerschenson M, Erhart SW, Paik CY, et al. **Fetal mitochondrial heart and skeletal muscle damage in erythrocytes patas monkeys exposed in utero to 3'-azido-3'-deoxythymidine.** *AIDS Res Human Retroviruses* 2000;16:635–644
- Gerschenson M, Nguyen V, Ewings EL, et al. **Mitochondrial toxicity in fetal erythrocytes patas monkeys exposed transplacentally to zidovudine + lamivudine.** *AIDS Res Human Retroviruses* 2004;20:91–100
- Poirier MC, Dive RL, Al-Harti L, et al. **Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers.** *J Acquir Immune Defic Syndr* 2003;33:175–183
- Alimenti A, Burge D, Ogilvie A, et al. **Lactic acidemia in HIV infants exposed to perinatal antiretroviral therapy.** *Pediatr Infect Dis J* 2003;22:782–789
- The European Mode of Delivery Collaboration. **Elective caesarian section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomized clinical trial.** *Lancet* 1999;353:1035–1039

25. Anonymous. ACOG Committee opinion: scheduled cesarean delivery and the prevention of vertical transmission of HIV infection. Number 234, May 2000. *Int J Gynaecol Obstet* 2001;73:279–281
26. Ioannidid JP, Abrams EJ, Ammann A, et al. Perinatal transmission of human immunodeficiency virus type 1 by pregnant women with RNA virus loads <1000 copies/mL. *J Infect Dis* 2001;183:539–545
27. Beasley RP, Hwang LY, Lee, GC-Y, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and Hepatitis B vaccine *Lancet* 1983;2:1099–1102
28. Centers for Disease Control. Protection against viral hepatitis. *MMWR Morb Mortal Wkly Rep* 1990;39:1–26
29. Mofenson L. Perinatal exposure to zidovudine: benefits and risks *N Engl J Med* 2000;343:803–805

In Vivo Neuroanatomy and Objectivity

An article on neuroanatomy may not be the highest priority in our daily deluge of reading material; what part of human anatomy is new, anyway? Hasn't it all been pretty well described (and learned) by now? Didn't Vesalius and da Vinci put all this to rest centuries ago?

There's always room for fine-tuning. The article in this month's *AJNR* by Demondion et al refocuses our attention on an anatomic area we might have thought we already knew pretty well. The reason to look more deeply into the neuroanatomy of the dorsal root of the spinal nerve lies in the increasing frequency with which interventional neuroradiologists are asked to access those structures to provide pain relief and deliver a more precise preoperative diagnosis and help ensure successful ultimate surgical outcomes. Demondion et al point out the pertinent anatomy of the region of the dorsal root and locations of exact nerve injection sites useful for CT or fluoroscopic guidance. Excellent CT and gross anatomic sections correspond with sharp photographic details of the posterior ramus, dorsal root ganglion, and associated tissues. Theirs is a nice, detailed piece of work, especially the images.

The imaging techniques, CT and fluoroscopy (or CT fluoroscopy), and the depiction of the pertinent neuroanatomy are what separate the neuroradiologist as pain therapists from the other specialists who perform these nerve root blocks and facet blocks blindly, by using surface anatomic features. It would be hoped that our approach might yield better results in evi-

dence-based medicine, but of course, this all remains to be proved, one hopes, by large clinical trials by the next generation of neuroradiologists.

With reference to the specific application of the anatomic information contained in this article to the art of spinal nerve root sleeve blocks and facet blocks, this detailed information will help the practitioner increase his or her accuracy and possibly stay out of trouble. It is often unavoidable not to place a needle tip into one of those small blood vessels that inhabit the nerve root foramen, but it is important to know they might be there and to take some steps to be sure your needle is not in one before injection. This can take the form of simply drawing back on the needle to see whether there is any blood flow or a test injection of a tiny amount of nonionic contrast medium before the lidocaine or steroid injection. Also, knowing the relative size of the nerve root foramen or the capacity of the facet joint that is the target structure is always helpful in choosing the optimal amount of contrast material to inject, because one seeks to inject enough to get the job done but not too much to flood the region and render the specificity of the targeted injection moot.

So, neuroanatomy is important, and good solid basic scientific articles like this one need to be part of our continued reevaluation of the human nervous system.

F. REED MURTAGH
Member, Editorial Board

“Dilated Perivascular Spaces: A Hallmark of Mild Traumatic Brain Injury”—A New Paradigm?

The ability to diagnose moderate to severe intracranial trauma accurately has traditionally been the domain of CT in the emergent setting (1). MR imaging has enhanced diagnosing shearing injuries (gradient echo imaging), subtle extraaxial hemorrhages (secondary to its multiplanar capabilities and superb soft tissue contrast), and subarachnoid hemorrhage (fluid-attenuated inversion recovery [FLAIR] pulse sequence). Even so, the ability to detect mild and subtle trauma continues to be an enigma. In this issue of the *AJNR*, Inglese et al have elegantly described that dilated perivascular spaces (PVSs, also known as Vir-

chow-Robin spaces) in the deep white matter on T2-weighted images are often seen in patients with mild traumatic brain injury (TBI), a finding not previously reported. Enlarged PVS was defined as greater than 2 mm. The authors also proposed that an inflammatory component is a contributing etiology to the dilated PVS.

This study compared MR findings in 24 patients, 18–50 years of age, with mild TBI, along with a control group. The TBI group was further subdivided into early MR imaging (15 patients imaged 1–9 days from the date of the initial trauma) and late MR

imaging (nine patients imaged 0.6–13.4 years from the date of initial trauma), with the control group similarly subdivided. The number of dilated PVSs was analyzed as were cerebral and CSF volumes. Thin-section MR imaging (3-mm contiguous cuts) with a high matrix was obtained on a 1.5T unit using T1-weighted, T2-weighted, and FLAIR pulse sequences with volumetric image analysis performed on a Sun workstation with in-house–developed Multimodal Image Data Analysis System (MIDAS) software. The average number of PVSs in TBI patients was significantly higher (7.1) than in the control group (2.4). The number of PVSs did not correlate with brain or CSF volumes, the age of the patients, or the elapsed time from injury in the TBI group, reflecting early and permanent brain changes.

The etiology for dilated PVS is nonspecific and has been described in the normal population. It has been associated with aging, neurosarcoidosis, cryptococcus, mucopolysaccharidosis, and recently, in early MS (2). Dilated PVS as a marker for early and permanent findings in patients with mild TBI is novel and may add to the radiologic imaging armamentarium; however before this becomes dogma, more-detailed analysis is needed. The authors examined only 24 patients and lacked baseline MR imaging studies before the trauma and neuropsychological testing, factors they have acknowledged. Serial studies with larger numbers are needed to validate the authors' findings. Retrospective studies analyzing for dilated PVS in both mild and severe trauma will also be helpful. The study is further limited because contiguous 3-mm sections without interleaving were obtained; the potential for cross-talk artifact was not addressed.

Diffusion Tensor Tractography: Exploring the Cost-Benefit Ratio of Incorporating CSF Suppression into Fiber Tracing Algorithms

Recent advances in the imaging of water diffusion have led to the development of diffusion tensor imaging (DTI) (1–3), which uses the properties of water diffusion to provide information about the integrity, location and orientation of white-matter tracts in brain. DTI presents an exciting new opportunity not only for examining brain microstructure in various disease states, but also for studying functional connectivity.

DTI exploits the fact that diffusion of water molecules in white matter is constrained, or anisotropic, moving preferentially along the primary axes of fiber tracts. Diffusion tensor data are represented in each voxel as a 3D ellipsoid, reflecting the rate of diffusion along the ellipsoid's three principal axes. Voxels along fiber pathways tend to form lines along these pathways. By connecting the long axis of each ellipsoid between given starting and end positions, one can trace the structure of fiber tracts.

There are several problems associated with quantita-

The etiology of dilated PVS with TBI is speculative. The authors provide references to experimental and human studies to support the theory of the inflammatory cascade being at least a contributing factor for enlarged PVS in patients with mild TBI, superimposed on shear strain as the etiology (3, 4). The authors state that histologic data are missing and that further work is necessary. Imagine the possibility of limiting or negating the traumatic brain response with early antiinflammatory treatment. Inglese et al predict that the use of higher-field-strength magnets with a higher matrix or resolution will lead to better visualization and quantification of high convexity VRS. This manuscript "stirs the pot," both from an imaging point of view and in terms of potential therapeutic treatment of mild posttraumatic findings depicted by MR imaging.

GREGORY CHALJUB

Guest Editor

Department of Radiology

University of Texas Medical Branch

Galveston, TX

References

1. Crow WN. Aspects of neuroradiology of head injury. *Neurosurg Clin North Am* 1991;2:321–339
2. Achiron A, Faibel M. Sandlike appearance of Virchow-Robin spaces in early multiple sclerosis: a novel neuroangiographic marker. *AJNR Am J Neuroradiol* 2002;23:376–380
3. Schoette RJ, Kochanek PM, Magargee MJ, et al. Early polymorphonuclear leukocyte accumulation correlates with the development of posttraumatic cerebral edema in rats. *J Neurotrauma* 1990;7:207–217
4. Holmin S, Soderlund J, Biberfeld P, Mathiesen T. Intracerebral inflammation after human brain contusion. *Neurosurgery* 1998;42:291–298

tive DTI tractography which need addressing before fiber tractography becomes a clinical reality. For instance, there is no reference standard yet for *in vivo* tractography. DTI requires extensive computing power, man-hours, and expertise. DTI also suffers from the same artifacts and limitations associated with acquiring DWI data, including motion artifact-induced ghosting, eddy current misregistration errors, and signal intensity loss due to susceptibility variations.

In the March issue of the AJNR, Chou et al (4) address an important aspect of susceptibility artifact in DT tractography by investigating the effects of CSF suppression by using FLAIR in normal adult brains. Drawing on the experience of DWI studies, they compare diffusion tractography incorporating FLAIR with DT tractography based on conventional spin-echo echo-planar technique. Several DWI studies have already shown that partial volume effects from CSF result in overestimation of ADC and underestimation of diffusion anisotropy in regions prone to

partial volume effects. Many of these same studies also show that suppressing CSF signals by incorporating FLAIR eliminates many of the inaccuracies in ADC and anisotropy measurements in susceptible brain regions (5–7).

The authors hypothesize that diffusion-tensor tractography might benefit from CSF suppression in susceptible brain regions since fractional anisotropy measurements also show improvement. Fiber tracking algorithms are however strongly dependent on SNR, which is diminished with FLAIR. Therefore, the premise of Chou et al's study is to investigate whether there is any net benefit in incorporating FLAIR into DTI fiber tracking, since the benefits from improved anisotropy measurements may be offset by loss of SNR.

In their study, Chou et al demonstrate a clear advantage in using CSF suppression for detecting fiber tract volume in periventricular regions. What remains to be determined, however, is whether the loss in SNR with FLAIR limits tractography in regions relatively free of CSF contamination. Whereas SNR is not as important in the calculation of diffusion coefficient values with conventional DWI, it is perhaps the most important determinate in fiber tracking, aside from anisotropy measurements.

The incorporation of CSF suppression for tractography may ultimately be used in a situation-specific manner, depending on the specific research or clinical

question at hand. Chou et al's thorough study presents a first convincing argument for the role of CSF suppression in tractography involving periventricular pathways. It will be important to learn whether CSF suppression limits or facilitates tractography in other brain regions likely to be involved in various disease states, injury, aging, and functional studies.

CHRISTOPHER D. LASCOLA

Guest Editorialist

*Brain Imaging and Analysis Center
Duke University Medical Center*

References

1. Xue R, van Zijl PC, Crain BJ, Solaiyappan M, Mori S. **In vivo three-dimensional reconstruction of rat brain axonal projections by diffusion tensor imaging.** *Magn Reson Med* 1999;6:1123–1127
2. Poupon C, Clark CA, Frouin V, et al. **Regularization of diffusion-based direction maps for the tracking of brain white matter fascicles.** *Neuroimage* 2000;12:185–195
3. Basser PJ, Pajevik S, Pierpaoli C, Duda J, Aldroubi A. **In vivo fiber tractography using DT-MRI data.** *Magn Reson Med* 2000;44:625–632
4. Chou MC, Lin YR, Huang TY, et al. **FLAIR Diffusion-Tensor MR Tractography: Comparison of Fiber Tracking with Conventional Imaging.** *AJNR Am J Neuroradiol* 2005;26:591–597
5. Hirsch JG, Bock M, Essig M, Schad LR. **Comparison of diffusion anisotropy measurements in combination with the FLAIR technique.** *Magn Reson Imaging* 1999;17:705–716
6. Papadakis NG, Martin KM, Mustafa MH, et al. **Study of the effect of CSF suppression on white matter diffusion anisotropy mapping of healthy human brain.** *Magn Reson Med* 2002;48:394–398
7. Ma X, Kadak YM, La Carte SM, Hu X. **Enhancing measured diffusion anisotropy in gray matter by eliminating CSF contamination with FLAIR.** *Magn Reson Med* 2004;51:423–427