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Abnormal Findings of Head Magnetic Resonance Imaging in Two Siblings Born to an HIV-Positive Woman

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The Preventing Mother-to-Child Transmission (PMTCT) program for human immunodeficiency virus (HIV) has reduced the vertical transmission rate (1). In developed countries, this program can reduce the risk of vertical transmission from 20% to below 1% (1). However, antiretroviral drugs used for the PMTCT program such as zidovudine (AZT) are toxic to mitochondria. Although AZT is one of the main drugs for prophylaxis of vertical transmission, approximately 1% of children who are administered AZT develop neurological symptoms due to mitochondrial dysfunction (2,3). Patients who suffer from mitochondrial dysfunction can have various symptoms, including mental retardation, spasms, and hypermyotonia/hypomyotonia. Their clinical examinations also show a variety of abnormal findings, such as lactic acidosis, abnormalities in head imaging, and abnormal electroencephalograms (2,3).

To date, the effect of HIV virus itself and antiretroviral drugs on mental development of children born to HIV-positive women is not apparent. However, antiretroviral therapy (ART) for PMTCT might impair children’s neurological development. The Japanese protocol guidelines currently recommends PCR diagnostic tests, repeated 4 times, until 4 to 6 months of age for infants born to HIV-positive mothers. However, there is no definite recommendation on the duration of clinical observation after the PMTCT program (4).

We evaluated 2 siblings (Cases 1 and 2) who were born to an HIV-positive mother and presented with abnormal findings of magnetic resonance imaging (MRI) of the head. The older sibling (Case 1) showed major developmental delay at the age of 3 years. This brief note reports on their details.

The siblings’ mother was from a country in South East Asia, and she was 39 years old (gravida 0, para 0). She presented to our Obstetrics/Gynecology Department at 11 weeks of gestational age in 2007. Her HIV serostatus was confirmed as positive at her initial visit. She was an intravenous drug user. At 17 weeks of gestational age, her AIDS Clinical Center commenced ART (with lopinavir/ritonavir, lamivudine, and abacavir). At the beginning of ART, her CD4 level was 34/μl and viral load was $1.6 \times 10^4$ copies/ml. However, at the time of delivery of Case 2, her CD4 level was 364/μl, and viral load was negative. She had no other history or family history of clinical significance. Her husband is Japanese and had no history of clinical significance.

The Japanese PMTCT protocol does not recommend breastfeeding. Our protocol includes continuation of maternal ART, intravenous administration of AZT during delivery, and oral administration of AZT to neonates for 6 weeks (4). Our guideline also recommends delivery by cesarean section. In our patients, PMTCT was conducted based on our domestic guideline.

Case 1 was a male infant born at 37 0/7 weeks, and birth weight was 2,181 g (light-for-date). Autistic tendencies were observed at 3 years of age, with no utterance at age 5 years, 6 months. Brain MRI findings at age 15 months showed a T2 extension area on both sides of the parietal lobe (Fig. 1A). Case 2 was a female in-
fant born at 36 1/7 weeks, and birth weight was 2,310 g (appropriate-for-date). Mental development was within normal limits at 2 years of age. Nevertheless, T2 extension areas on both sides of the frontal parietal white matter were found in head MRI at 17 months of age (Fig. 1B). In both cases, T2 extension areas regressed during the years of follow-up (Fig. 2). Developmental delay of Case 1 remained with no aggravation. Case 2 showed normal developmental growth. Outpatient follow-up was continued until March 2014.

To the best of our knowledge, causality between AZT administration and neurological symptoms has not been established. Furthermore, HIV infection itself might impair mitochondrial DNA (5). The differences between Case 1 and Case 2 also might be explained by the situation of maternal HIV infection at each delivery because untreated maternal HIV infection increases stillbirths, preterm delivery, low birth weight, and so on (6). Additionally, the intrinsic cause of mental retardation other than AZT and HIV infection needs to be considered. Therefore, it seems difficult to determine what causes such abnormalities.

Nevertheless, it seems to be rather reasonable for us to attribute these MRI findings abnormalities in these 2 patients to exposure to AZT during their neonatal period, rather than to genetic or metabolic causes. Poirier et al. also pointed out that it is difficult to ascertain whether the presence of maternal HIV-1 infection, or the antiretroviral drugs given to prevent MTCT, or both, are major causative events of mitochondrial dysfunction. In children born to HIV-1-infected mothers, however, they insisted that nucleoside reverse transcriptase inhibitors (NRTIs), like AZT, might cause mitochondrial dysfunction even in patients without detectable HIV (7). Additionally, it was also reported that NRTI might induce mitochondrial compromise in the brain (8). High-intensity lesions in both sides of periventricular white matter are compatible with brain MRI findings of mitochondrial encephalopathy (9). Recently, the United States recommended 4 weeks of AZT prophylaxis for infants (10), in cases in which maternal HIV infection is appropriately treated, and as Ferguson et al. demonstrated (11), a 4 week regimen might be as effective as one of 6 weeks duration. It seems to be time for us to consider a shorter duration of AZT prophylaxis.

Needless to say, we cannot completely deny that other intrinsic reasons such as metabolic disorder could explain these findings, because we have no direct and definite evidence that can relate these findings to AZT administration. However, we believe that it is a more persuasive idea that a common medication for these 2 cases had an influence on their similar abnormality, rather than that some primary dysfunction occurred in these 2 siblings by chance.

Notably, autistic tendencies in Case 1 were recognized at 3 years of age, and Case 2 might demonstrate developmental delay in the future. In France, long-term neurological dysfunction was reported as a severe adverse effect of AZT exposure in perinatal period (12). Therefore, a careful and long-term clinical follow-up is necessary for children who are born to HIV-positive mothers and receive ART for PMTCT, even if their serostatus is negative.

As we discussed above, although the effect of PMTCT programs in developed countries is well established, these programs might have an unfavorable effect on neurological prognosis. Further accumulation and long-term observation of cases are desirable for the safety of children born to HIV-positive mothers.

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Conflict of interest None to declare.

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