Seizures in a neonate on zidovudine prophylaxis

Infants exposed to human immunodeficiency virus (HIV) should receive postpartum antiretroviral therapy to reduce mother-to-child transmission of the virus. This report describes the occurrence of seizures in a neonate on zidovudine (azidothymidine, AZT) prophylaxis born to an HIV positive mother.

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Key points

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1. Antiretroviral therapy significantly reduces the risk of mother-to-child transmission of HIV infection.
2. The benefits of neonatal post-exposure prophylaxis far outweigh the potential for adverse effects.
3. There is a need for vigilance for neurodevelopment outcome in infants on retroviral prophylaxis and establishment of a surveillance protocol.

A female infant was born to a mother infected with HIV. The mother had a low viral load throughout pregnancy (50-100 copies/mL) with a CD4 cell count of 320 cells/mm^3 of blood (CD4/CD8 ratio = 23%). The mother had been compliant with her antiretroviral therapy (ART) since the second trimester of pregnancy: Combivir® (zidovudine and lamivudine) and Kaletra (lopinavir and ritonavir). The mother's blood tests and antenatal scans were normal and there was an uneventful perinatal period.

The infant was born at term by an elective caesarean section with intact membranes. She had a birthweight of 3.15kg (25th centile) with Apgar scores of 9 at one and five minutes. After blood sampling for a full blood count and HIV PCR (polymerase chain reaction) testing, the infant was started on oral zidovudine monotherapy (4mg/kg, twice daily) and then discharged home. She was bottle fed and remained well at home.

At birth the infant's HIV status was indeterminate. Her test results were:

- HIV-1: preliminary positive result ('reactive')
- HIV-2: negative
- HIV-1 nucleic acid-based test: negative

At 3.5 weeks of age, the infant presented to the emergency department with seizures. The mother reported one episode of generalised-tonic posturing/stiffening of all limbs with up-rolling of the eyes, lasting for approximately 30 minutes. A second episode was recorded in hospital. Upon examination, the infant's head circumference measured 36cm (50th centile); she weighed 3.98kg (25-50th centile) and had a temperature of 36.5°C. The general and neurological examinations were normal. The results of laboratory investigations can be seen in **TABLE 1**.

The infant was given a loading dose of phenobarbital to treat her seizures and was started on antibiotics (benzylpenicillin and gentamicin) and acyclovir in case of infection. She had a few short-lasting seizures in the first 12 hours of admission, which subsided without any intervention. Oral feeds and oral medication, including zidovudine, were stopped during her hospital stay.

Following normal test results (**TABLE 1**), antibiotic and acyclovir treatment was stopped. The infant was discharged with an outpatient appointment for magnetic resonance imaging (MRI) and an electroencephalogram (EEG). Upon discussion with the infectious disease team, it was decided to recommence oral zidovudine on discharge, pending the results of HIV PCR testing.

Three days later the infant was readmitted with a similar history. Again, the systemic examination was normal, another full septic screen was performed and antibiotic and acyclovir therapy was restarted. The infant received another loading dose of phenobarbital and the seizures gradually subsided over the following 12 hours. All of the repeat tests were normal including the head MRI and EEG.

Neonatal post-exposure prophylaxis for HIV is normally given for four weeks but, because the infant had periods of no medication, it was decided to continue zidovudine therapy until she reached one month of age. At this point, her HIV status was negative (ie negative for HIV-1, HIV-2,

Investigation	Result (normal range in brackets)
Haemoglobin level, white blood cell count, neutrophil count	Considered normal
Full septic screen	Considered normal
Capillary blood glucose measurement	4.5mmol/L
Sodium	139 (136-146mmol/L)
Potassium	4.2 (3.5-5.1mmol/L)
Urea	1.6 (2.4-6.2mmol/L)
Creatinine	28 (26-63μmol/L)
Calcium	2.48 (2.16-2.43mmol/L)
Phosphate	2.12 (1.24-2.51mmol/L)
Magnesium	0.82 (0.75-1.2mmol/L)
Alkaline phosphatase (ALP)	192 (128-292U/L)
Albumin	33 (34-52g/L)
C-reactive protein (CRP)	<5 (0-10.1mg/L)
Alanine transaminase (ALT)	29 (4-46U/L)
Lactate	1.5mmol/L
Capillary blood gas measurement	pH 7.38 pCO_2: 5.2kPa pO_2: 6.3kPa B.E. (base excess): 0.1mmol/L
Ionised calcium (iCa)	1.53mmol/L
Blood and cerebrospinal fluid (CSF) cultures	Negative
Viral screen (PCR) for enterovirus, herpes simplex virus (HSV-1 and HSV-2) and varicella zoster virus (VZV)	Negative
Serum amino acid profile	Normal
Urine organic acid profile	Normal
Urinary alpha aminoadipic acid (a biomarker for pyridoxine-dependent seizures)	Normal
Cranial ultrasound scan	Normal
MRI scan	Normal
EEG scan	Normal

TABLE 1 Investigations performed around the time of presentation with seizures.

p24 protein of HIV and HIV proviral DNA) and zidovudine was discontinued.

The infant had no further seizures. Follow-up examinations at six weeks and six months were normal; she was growing well with normal developmental milestones and a head circumference of 42.3cm (50th centile).

Discussion

Zidovudine has significantly reduced the risk of mother-to-child transmission of HIV infection[1]. The British HIV Association (BHIVA) guideline at the time of treatment recommended zidovudine monotherapy and pre-labour caesarean section for all asymptomatic HIV positive women with low plasma viral loads[2].

A decade ago an overwhelming HIV disease load and immense pressure to control this potentially fatal viral infection justified the widespread use of antiretroviral drugs, despite the paucity of safety data for infants exposed *in utero*. With evolution of combination ART, mortality has decreased and attention has now moved to studies of the outcomes of treatment.

There are reports showing impaired psychomotor development and seizures in uninfected children at six months of age, possibly secondary to zidovudine-induced mitochondrial dysfunction[3,4]. Fortunately, follow-up did not show any permanent neurological problems at 18 months of age, implying temporary mitochondrial dysfunction. There are similar reports of an increased risk of seizures in adults and febrile seizures in children following the use of zidovudine for post-exposure prophylaxis, however it is difficult to validate a cause-effect relationship with zidovudine because of the multiple confounding factors[5,6].

Two mechanisms have been proposed for these neurological effects. Firstly, mitochondrial DNA mutation in the placenta affecting respiratory chain function and secondly, mutation on exposure to antiretroviral drugs of rapidly dividing cells (eg nervous tissue, haematopoietic cells and liver cells)[7,8].

In the case presented here, no specific cause could be found for the seizures in the infant and the possibility of medication-induced seizures secondary to zidovudine was considered. It is possible that this was an incidental finding but the subsidence of seizures and the normal investigations and neurodevelopment following cessation of zidovudine therapy support the consideration. The investigations carried out gave no reasons to clinically suspect congenital infection or genetic, metabolic or structural causes.

The case presented here is unique in terms of the early age of seizure onset. A literature search revealed no other reports of neurological adverse effects secondary to zidovudine in the neonatal period. Although the benefits of antiretroviral prophylaxis in prevention of mother-to-child transmission of HIV far outweigh the potential for adverse effects, the case highlights the need for vigilance for neurodevelopment outcome in infants on retroviral prophylaxis and establishment of a surveillance protocol.

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