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Publication Date

2022

DOI

10.1177/2050313x221142236

SAGE Open Medical Case Reports
Volume 10: 1–4

DOI: 10.1177/2050313X221142236
journals.sagepub.com/home/sco
SAGE

Rapid neurodevelopmental recovery after ART initiation in an infant with HIV encephalopathy

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Abstract

While there is ample evidence that antiretroviral therapy (ART) can improve cognitive outcomes in older children living with HIV, encephalopathy in infants has historically been considered an advanced disease presentation with less likelihood of neurodevelopmental recovery on treatment. More recent studies suggest that timely ART can halt encephalopathic disease progression and even lead to symptom resolution. Here we present a case of an HIV-positive infant diagnosed with encephalopathy who experienced impressive and rapid improvement with a multi-disciplinary care approach that included physical and occupational therapy and ART.

Keywords

HIV, encephalopathy, infant, ART

Date received: 8 August 2022; accepted: 10 November 2022

Introduction

HIV encephalopathy (HIVE) is an AIDS-defining clinical condition in children for which the World Health Organization (WHO) provides clinical diagnostic criteria that include developmental delay or regression, acquired central motor deficits, and impaired brain growth. The WHO criteria for definitive diagnosis is neuroimaging that demonstrates cerebral atrophy and basal ganglia calcification.[1] The risk for development of HIVE is greatest in infants, with a reported 10% incidence in perinatally infected patients, and up to half of all children with HIVE will have signs or symptoms by 12 months of age.[2–4]

Several early studies on the impact of antiretroviral therapy (ART) on HIVE suggested that progression of HIVE could be halted, but that recovery was less likely with patients more typically having static, plateau, or sub-acute progressive neurodevelopmental evolution.[5–10] However, more recent research has reported that HIVE can improve or even resolve with early and effective ART.[10–12] Here we present the case of an HIV-infected infant diagnosed with HIVE at 9 months of age who showed dramatic neurologic improvement after 6 months on ART.

Case report

A 9-month-old female presented to Hospital Central de Maputo with 3 days of cough which progressed to respiratory distress, poor oral intake, fever, lethargy, and white oral plaques. She was hypoxic with oxygen saturations of 85% on room air with tachypnea and subcostal retractions. Her admission laboratory included a full blood count with leukocytes of 18.7×10^3 cells/uL, hemoglobin of 7.3 g/dL, and platelets of 73×10^3/uL, and a biochemistry panel with normal creatinine, transaminases, and basic electrolytes. She

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was diagnosed with severe pneumonia, oral candidiasis, moderate anemia, and severe acute malnutrition (weight for height Z score = 0.1 percentile), admitted, and started on oxygen supplementation, intravenous antibiotics and antifungal therapy, and therapeutic milk.

The mother was HIV-positive and had been on antiretroviral treatment (ART) for 7 years, but due to nausea and vomiting during the first trimester of pregnancy she stopped taking her regimen of tenofovir/lamivudine/dolutegravir and did not resume treatment after birth. She reported an uncomplicated pregnancy and vaginal delivery at 41 weeks of gestation, with APGAR scores of 8 and 9 at 1 and 5 min, respectively.[13] The infant received post-natal prophylaxis with 6 weeks of zidovudine and 12 weeks of nevirapine treatment for prevention of mother to child transmission of HIV (PMTCT). She had a negative DNA polymerase chain reaction (PCR) test at 1 month of age and was initiated on cotrimoxazole prophylaxis. She was breastfeeding and in HIV-exposed infant follow-up care until the age of 6 months, after which time she was lost to follow-up. There were no prior hospitalizations and no known tuberculosis (TB) contacts.

Given the history and clinical presentation at admission, a point-of-care HIV nucleic acid test was ordered and returned positive. With this finding, and a chest radiograph that had bilateral interstitial opacities, treatment for *Pneumocystis jirovecii* and cytomegalovirus were added. Her baseline HIV RNA PCR viral load was >1,000,000 copies/mL, and she had severe immune suppression with a CD4 cell count of 280 cell/mm^3 and 23%. COVID-19 PCR was negative as were TB diagnostic tests including Xpert MTB/Rif® (on nasopharyngeal aspirate and stool specimens) and urine lipoarabinomannan (LAM).

On developmental history, the mother reported that she was initially meeting most age-specific developmental milestones until 6 months of age. She tracked objects across visual field at 2 months, had full head control at 3 months, sat with assistance at 5 months, and sat independently at 6 months. After 6 months of age, the patient started to regress with loss of development milestones, and prior to admission she could no longer sit independently and lost head control. The mother also reported progressive weakness, apathy, and decreased interactivity, but denied any focal neurologic deficits or history of seizures.

On her intake neurologic examination, she was responsive but lethargic. There was significant bilateral upper extremity hypertonicity, bilateral hyperreflexia of the biceps tendons, and mild axial hypotonia. Lower extremity tone and reflexes were normal. She had right eye divergent strabismus, but no other notable cranial nerve abnormalities. The anterior fontanelle was normotensive, and there was no nuchal rigidity. Head circumference was at the 8th percentile for age (42 cm), with a decrease in growth velocity based on previous measurements documented on the infant's health card. The remainder of the neurologic examination was within normal limits without any asymmetry noted. There was no history of seizures.

Supplementary examinations including neuroimaging (computerized tomography or magnetic resonance imaging) and toxoplasmosis and cytomegalovirus serologies were not available. However, based on the developmental regression and abnormal neurologic examination with pathological upper extremity reflexes and hypertonia, a clinical diagnosis of HIVE was made. She was discharged after 11 days of hospitalization with resolution of her respiratory illness and improvement in her nutritional status, but without any changes in her neurologic examination. ART was initiated on the day prior to discharge with a regimen of abacavir, lamivudine, and lopinavir/ritonavir (LPV/r).

After discharge, she was referred for physical and occupational therapy, outpatient nutritional rehabilitation, and maintained monthly outpatient follow-up for her HIV, with good reported ART adherence. She had one readmission at 11 months of age for acute gastroenteritis with dehydration for 7 days. After 12 months of age and 3 months on ART, her viral load had decreased to 729 copies/mL, her weight had increased from 5.1 to 7.0 kg, with normal acute nutritional status classified by weight for length Z score, and her head circumference for age was now in the 12th percentile. Developmentally, she had improved head control, was sitting independently in tripod position, displayed more social interaction, and showed age-appropriate separation anxiety. She was able to roll-over, was babbling, and had raking grasp, but was still not crawling, standing, or walking with support. On neurologic examination, she had improved axial hypotonia, with resolution of upper extremity hypertonia. Strabismus was unchanged.

At 15 months of age and 6 months on ART, she continued to gain weight and show neurodevelopmental improvement. She was now able to sit independently, stand and take a few steps with support, transfer objects between hands, and had two words that she routinely used. On examination, her axial muscular tone, appendicular muscular tone and reflexes were symmetric and intact, and her strabismus was less pronounced.

Discussion

This infant had a negative HIV virologic test at 1 month of age, normal growth and development in the first months of life, and was almost certainly infected through breastfeeding. Her presentation at the time of hospital admission at 9 months of age with severe malnutrition, opportunistic infections, and encephalopathy, with corresponding severe immune suppression and extremely high HIV viremia, is consistent with what is known about the particular vulnerability of infants to untreated HIV infection, with very high rates of associated morbidity and mortality.[14] In addition, her neurodevelopmental status at the time of HIV diagnosis with

global developmental delay and regression, decreased velocity of brain growth, and acquired central motor deficits is classic for the rapidly progressive form of HIV encephalopathy that has been described in untreated infants.[3,15]

Her impressive neurodevelopmental recovery after initiation of ART is consistent with recent evidence that suggests that early HIVE is not necessarily a static condition and that symptom improvement or resolution is possible.[10] One proposed mechanism for this type of improvement is suppression of central nervous system (CNS) HIV viral replication via the use of potent ART regimens with good CNS penetration, such as the LPV/r-based regimen which this patient received.[16,17] It is also believed that effective ART can improve impaired myelination that results from intrathecal inflammation caused by direct infection of CNS cells including microglia and astrocytes by HIV, causing the release of inflammatory cytokines.[10,18]

HIVE is a process that begins with more subtle signs and symptoms, and it is likely that this patient would have been diagnosed earlier had she not fallen out of outpatient care before admission to the hospital. Neurodevelopmental surveillance is crucial for the follow-up of HIV-exposed infants, and delays or regression should be triggers for repeat HIV testing. Once diagnosed with HIVE, a multidisciplinary care approach is recommended.[8,19,20]

Conclusion

Infants presenting with HIVE can experience rapid and impressive neurodevelopmental recovery using a multidisciplinary treatment approach that includes ART, physical and occupational therapy.

Acknowledgements

The Department of Pediatrics at the University of California Los Angeles David Geffen School of Medicine provided financial support for publication.

Author contributions

DQ, MS, UC, AP, SM, CB, and BE provided clinical care to the patient. MS and GS led manuscript drafting. All authors contributed to revisions and approved the final version.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Department of Pediatrics at the University of California Los Angeles David Geffen School of Medicine provided financial support for publication.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the mother of this patient to publish this case report.

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