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Late Onset HIV Encephalopathy in Children with Long-Standing Virologic Suppression Followed by Slow Spontaneous Recovery despite No Change in Antiretroviral Therapy - Four Case Reports

Steve Innes, MBBCh, MRCPCH, MPhil, PhD^{1,2,§}, Ronald van Toorn, MBChB, FCPaed(SA)², Kennedy Otjombe, MSc³, Els Dobbels, MBChB, FCPaed(SA), DCH (SA)¹, Gert van Zyl, MBChB, MMed, PhD⁴, Mark F. Cotton, MBChB, MMed, PhD, FCPaed(SA), DTM&H, DCH (SA)^{1,2}, and Barbara Laughton, MBChB, FCPaed(SA)^{1,2}

¹Children's Infectious Diseases Clinical Research Unit (KID-CRU), Stellenbosch University, Cape Town, South Africa

²Department of Paediatrics and Child Health, Tygerberg Children's Hospital, Cape Town, South Africa

³Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Soweto, South Africa

⁴Division of Medical Virology, Stellenbosch University and Tygerberg Academic Hospital, Cape Town, South Africa

Abstract

We describe four CHER (Children with HIV Early antiRetroviral therapy) trial participants with late-onset HIV encephalopathy despite long-standing viral suppression in blood and undetectable HIV DNA and RNA PCR in cerebrospinal fluid. Extensive investigations revealed no alternative etiology. Reassuringly, all four experienced slow spontaneous recovery despite no change in antiretroviral therapy. Virally-suppressed HIV-infected children remain at risk for fluctuating neurologic signs and symptoms.

Keywords

South Africa; pediatric HIV; CHER trial; cerebrospinal fluid; CSF

§Corresponding author: Steve Innes, Ward J8, Tygerberg Children's Hospital, Cape Town, South Africa. Tel: +27 21 938-4297/Fax: +27 21 938-4151/Cell: +27 74 764 5253/ innes@sun.ac.za.

Conflicts of Interest

The authors have no competing interests to declare.

Authors' contributions

All authors contributed intellectually to the manuscript. SI, ED, MFC and BL provided medical care to patients. SI conceptualized the study, gathered data, compiled results and drafted the manuscript. KO helped to compile data and draft the manuscript. MFC and BL supervised data interpretation and manuscript drafting. RvT and GvZ provided specialist input (neurological and virological respectively) during medical care of patients and during data interpretation and manuscript drafting. All authors have read and approved the final manuscript.

Introduction

HIV encephalopathy (HIVE) is the most common neurologic manifestation of HIV in children and can be a presenting feature. Early administration of combination antiretroviral therapy (ART) dramatically reduces risk of HIVE in children especially when started soon after birth⁽¹⁾. Children may develop neurologic deterioration despite successful virologic suppression in peripheral blood⁽²⁾, traditionally attributed to continued HIV replication within the central nervous system (CNS), a known sanctuary site as described in adults⁽³⁾. We describe four children with long-standing virologic suppression who developed HIVE, which then slowly resolved without changes in ART regimens.

Methods

These 4 children were from the Cape Town site of the Children with HIV Early Antiretroviral therapy (CHER) trial⁽¹⁾ and remained in follow-up after the trial ended. In total, 52 children experienced some form of neurodevelopmental deterioration, of whom 26 met the study criteria for HIV encephalopathy and had no medical, psychosocial or nutritional causes other than HIV. Nine of those had undetectable viral loads before onset of neurodevelopmental deterioration, although only 4 children had lumbar punctures performed and are described here.

Annual assessment of gross motor, language, fine motor and personal-social developmental milestones using the Molteno Adapted Developmental Milestone Scale was performed⁽⁴⁾. More frequent neurodevelopmental assessments were performed when an abnormality was suspected, along with brain magnetic resonance imaging (MRI) and lumbar puncture where clinically indicated.

Diagnosis of HIVE required two of the following three criteria in the absence of an alternative etiology: (1) Acquired **cortical motor deficit** manifested as upper motor neuron (UMN) signs, specifically: pathologic reflexes (abnormally brisk reflexes *plus* abnormal spreading of reflexes, crossed adductor response or sustained clonus), increased tone, gait disturbance, ataxia or paresis, with evidence of previously normal neurologic examination; (2) **Impaired brain growth** manifested as acquired microcephaly (reduction in serial head circumference z-score of more than one standard deviation [SD] from baseline), or generalized brain atrophy on radiologic imaging; (3) Failure to attain or loss of **developmental milestones** on 2 consecutive visits, verified using the locally-developed Molteno Adapted Developmental Milestone Scale⁽⁴⁾, resulting in a developmental quotient (developmental age divided by chronologic age $\times 100$, equivalent to a percentage of expected for age) below 70 in a given developmental domain, with evidence of previously normal neurodevelopment of that domain. We defined normalization of the developmental quotient as return to 90. As per common practice, deep tendon reflexes are graded as: 0=absent; 1=slight but definitely present; 2=normal; 3=very brisk; 4=very brisk with spreading to adjacent joints or non-sustained clonus; 5=crossed adductor reflex or sustained clonus. Alternative etiologies were excluded after careful history, clinical, laboratory and radiologic investigation. In addition, psychosocial, maternal or nutritional causes were excluded. Quantitative HIV RNA testing in plasma using a Roche AmpliPrep/Cobas Amplicor assay

(Roche Molecular Systems, Pleasanton, California) with a lower limit of detection 20 copies/ml was measured retrospectively in at least two stored specimens per child, collected prior to onset of neurodevelopmental deterioration. HIV viral load testing in cerebrospinal fluid (CSF) was performed using the Nuclisens EasyQ® v1.2 assay (BioMérieux, Boxtel, Netherlands) with lower limit of detection is 50 copies/ml. For confirmation, CSF DNA and RNA were extracted using the Nuclisense EasyMag extraction kit (BioMérieux, Lyon, France) and PCR amplified using a previously described nested PCR and automated DNA sequencing method to amplify and sequence HIV-1 subtype C *tat*⁽⁵⁾.

Case descriptions

Participant characteristics are presented in Supplemental Digital Content 1 (Table). All cases were term deliveries with no perinatal concerns. Timelines of events are presented in figure 1.

Patient A

Patient A commenced ART at 8 weeks of age. Plasma HIV RNA was undetectable 5½ months later (aged 7½ months) and no blips were recorded during the next 66 months.

At 31 months of age, grade 3 deep tendon reflexes were noted in both lower and upper limbs when gross motor delay was also observed. By 36 months of age, his gross motor developmental quotient was 67 (compared to 100 at 9 months). Neurologic examination revealed grade 5 reflexes, unsteady gait and increased muscle tone in all limbs. Head circumference growth plateaued and z-score declined by 0.8 SD between 20 and 56 months of age. A brain MRI performed at 35 months of age revealed bilateral frontal and peritrigonal hyperintensities involving the subcortical and deep white matter.

Slow spontaneous improvement in gross motor function was observed with normalization after 10 months. At 42 months of age, after gross motor development had normalized, a high blood lactate level (4.2mmol/l) precipitated switching from zidovudine to abacavir. CSF lactate was 2.1mmol/l. Thereafter, the blood lactate gradually declined to 3.1mmol/l by 49 months and 1.9mmol/l by 64 months. UMN signs began to improve at 58 months and resolved by 79 months (6½ years of age). Recovery of gross motor milestones before resolution of UMN signs is clinically plausible.

Patient B

Patient B commenced ART at 15 months of age. Plasma HIV RNA was undetectable 5 months later (aged 20 months) and no blips were recorded during the next 64 months.

New UMN signs were observed at 54 months of age, worsening progressively over the following 8 months. She developed spasticity in lower limbs and grade 4 reflexes (symmetrical) in upper limbs. By 61 months of age her gross motor developmental quotient had dropped to 65 (compared to 100 at 54 months), including losing a previously-attained gross motor milestone: the ability to stand on 1 leg for 10 seconds. Head circumference growth plateaued and z-score dropped by 1.3 SD between 34 and 56 months of age. Brain MRI at 62 months of age showed no abnormalities. Her ART regimen was not changed.

Slow spontaneous improvement was observed over the following 6 months with gross motor developmental quotient improving to 90 by 67 months of age. There was a lag in improvement in UMN signs which was noted at 70 months with resolution by 73 months (6 years of age).

Patient C

Patient C commenced ART at 8 weeks of age. Plasma HIV RNA was undetectable 5 months later (aged 7 months); rebounded briefly to log 4.6 at 12 months but was undetectable shortly thereafter. She remained virally suppressed during the next 64 months apart from 2 short-lived viral blips (<200 copies/ml) at 34 and 41 months of age.

At 16 months of age her gross motor and language developmental quotients had deteriorated to 69 and 63 (compared to 89 and 94 at 9 months respectively). A month later, both gross motor and language quotients deteriorated to 60. Specifically, she used no words with meaning at 16 months of age; had a vocabulary of only 5 words with meaning at 20 months of age; and was unable to point to or identify a common object at 20 months of age. A hearing test was normal. Head circumference growth plateaued and z-score dropped by 1.4 SD between 1.0 and 55 months of age. Her brain MRI at 42 months of age was normal. ART regimen was not changed. Her gross motor and language functions gradually improved to normal by 36 and 53 months of age respectively. Her deep tendon reflexes had normalized by 53 months of age.

Patient D

Patient A commenced ART at 10 weeks of age. Plasma HIV RNA was undetectable 5 months later (aged 7½ months) and no blips were recorded during the next 66 months.

At 19 months of age, her gross motor developmental quotient was 63 (compared to 100 at 9 months). Despite a normal hearing test, her language developmental quotient had dropped to 58 (compared to 100 at 9 months): She had stopped babbling and had a vocabulary of 3 words, increasing to 9 words by 29 months of age. New UMN signs were observed at 30 months of age, with grade 4 reflexes (symmetrical) and increased tone in all 4 limbs. Head circumference growth plateaued and z-score dropped by 1.5 SD between 11 and 44 months of age. Brain MRI at 31 months of age was normal. Her language development began to improve from 30 months of age and was age-appropriate by 40 months. Her gross motor function gradually normalised by 40 months of age. Improvement in UMN signs was first noted at 55 months with resolution by 90 months (7½ years of age). Of note, she had a single uncomplicated, febrile seizure at 41 months of age.

All 4 cases

For HIV, no RNA or *tat* DNA were found in CSF. Other tests are listed in Supplemental Digital Content 1 (table). Gradual spontaneous recovery in gross motor function occurred over 6 months to 2 years despite unchanged ART (figure 2). UMN signs resolved far slowly over 3–5 years (figure 2).

Discussion

These case reports suggest that children receiving ART can experience neurologic deterioration and recovery *despite persistent viral suppression*. There are a number of possible reasons for these observations:

New-onset HIVE has been reported in children with undetectable plasma HIV RNA where neurologic deterioration was presumed to be driven by CNS viral replication⁽²⁾. To our knowledge, the current case descriptions are the first to document the absence of HIV in CSF when neurodevelopmental deterioration has occurred despite long-standing plasma viral suppression. In addition, this is one of the first to describe gradual spontaneous resolution despite no change in ART regimen. A recent retrospective case series documented recovery of lower limb tone in a large proportion of HIVE patients. However it is unknown whether those individuals who resolved were virally suppressed at the onset of neuromotor deterioration⁽⁶⁾. In addition, no CSF investigations were performed.

It may be argued that the absence of HIV RNA in CSF obtained after onset of neurologic symptoms may not reliably indicate complete virologic suppression in brain tissue. However, CSF HIV RNA is highly correlated with brain tissue HIV RNA and is considered a reliable indicator in the absence of brain tissue specimens⁽⁷⁾. In addition, decline in CSF HIV RNA load is slow, so an undetectable cell-associated HIV-1 *tat* in CSF may indicate a wider virus-free window than in plasma⁽⁸⁾. Alternatively, unrecognized intercurrent encephalitis due to a co-pathogen such as mumps or enterovirus may produce similar signs. However, no clinical or CSF evidence of this was observed.

ART itself may be neurotoxic^(9, 10). Robertson et al documented improved neurocognitive functioning in adults with high CD4 after elective interruption of ART⁽¹⁰⁾. However, our patients displayed gradual spontaneous neurodevelopmental improvement despite continuing the same ART regimen apart from Patient A in whom zidovudine was replaced by abacavir when recovery had already begun. Mitochondrial dysfunction is associated with both HIV and antiretroviral exposure, particularly thymidine analogues such as zidovudine. However, serum lactate was normal in patients B, C and D (see table, Supplemental Digital Content 1). In patient A, mitochondrial dysfunction is unlikely to be the only reason for neurologic deterioration. None of our patients were on efavirenz, which has well-recognized neurotoxicity.

Neuronal injury may have occurred secondary to immune dysregulation. A correlation has been found between the severity of cognitive impairment and tumor necrosis factor elevation in brain astrocytes and microglial cells, as well as with the number of activated microglial cells, but not with the number of HIV-infected cells in brain tissue⁽¹¹⁾. The pathogenesis of some CNS damage may be mediated by over-production of inflammatory cytokines in response to components of non-viable HIV, particularly GP120⁽¹¹⁾. It is possible that inflammation may have caused Schwann cell injury and demyelination, followed by gradual recovery and remyelination. Inflammatory markers and absolute CD8 counts, which may have contributed to our understanding of mechanisms of injury were not routinely measured. Absolute CD8 counts in CSF could not be measured as body fluids other than blood are

routinely centrifuged before being analyzed, making an absolute cell count per μL unreliable.

These case report observations were only possible because of the patients' participation in a neurodevelopmental substudy; therefore we cannot comment on the frequency of this phenomenon and the incidence is unknown. However, this natural history should be borne in mind when interpreting interventional trials relating to HIVE⁽¹²⁾.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Timeline of events in Patient A

Timeline of events in Patient B

Timeline of events in Patient C

Timeline of events in Patient D

Figure 1.
Timeline of events for each case

Figure 2.

Pattern of deterioration and spontaneous slow improvement of gross motor abnormalities over time

Footnote to figure 2: Each node on the figure indicates the timing of a neurologic assessment. Where abnormalities were suspected, these were separately reviewed and confirmed by a neurodevelopmental paediatrician (BL).