CASE REPORT

Noncirrhotic portal hypertension in a human immunodeficiency virus (HIV) infected adolescent

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Abstract

Objective: To alert the pediatrician who is following up HIV-infected patients about the possibility of non-cirrhotic portal hypertension (NCPH) in this period of life, in order to avoid the catastrophic consequences of this disease as bleeding esophageal varices.

Case description: A 13 years old HIV-infected patient by vertical route was receiving didanosine (ddI) for 12 years. Although the HIV viral load had been undetectable for 12 years, this patient showed gradual decrease of CD4+ T cells, prolonged thrombocytopenia and high alkaline phosphatase. Physical examination detected splenomegaly, which triggered the investigation that led to the diagnosis of severe liver fibrosis by transient elastography, probably due to hepatic toxicity by prolonged use of ddI.

Comments: This is the first case of NCPH in HIV-infected adolescent described in Brazil. Although, the NCPH is a rare disease entity in seropositive patients in the pediatric age group, it should be investigated in patients on long-term ddI or presenting clinical and laboratories indicators of portal hypertension, as splenomegaly, thrombocytopenia and increased alkaline phosphatase.

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KEYWORDS
Acquired immunodeficiency syndrome; Liver cirrhosis; Didanosine/adverse effects; Adolescent

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Introduction

It is estimated that approximately 718,000 individuals live with HIV/AIDS in Brazil, representing a prevalence rate of 0.4% in the general population. AIDS detection rate in Brazil has increased about 2% in the last 10 years, especially among young individuals aged 15-24 years and adults aged 50 years or older. However, AIDS detection rate in children younger than five years old, an indicator used in Brazil to monitor HIV vertical transmission, decreased by 35.8% compared to 2003. The combined antiretroviral therapy (cART) resulted in a sharp decrease in mortality of children and adolescents infected with HIV. Nucleoside analogue reverse transcriptase inhibitors (NRTIs) were the first available antiretroviral drugs and it is not rare to find HIV-infected patients that have been using these drugs (alone or combined with other antiretroviral classes) for over 10 years.

Infectious diseases (including opportunistic infections) progressively decreased with treatment, but the non-infectious complications, including liver disease, have become significant causes of morbidity and mortality in the long-term among survivors. A retrospective study in South America (Brazil, Mexico, Argentina and Peru), including 6,000 HIV-positive adult patients, showed that terminal liver failure or cirrhosis was the leading cause of death, with 54/130 (42%) confirmed or probable cases based on clinical, laboratory or histological findings. The combined antiretroviral therapy with didanosine-ddI + Nelfinavir-NFV.

Non-cirrhotic Portal Hypertension (NCPH) is one of the clinical entities that affect HIV-infected patients. It is a rare disease, occurring in up to 0.5% of HIV-positive adult patients. The direct action of HIV itself, endothelial and mitochondrial damage, hypercoagulability and microbial translocation are factors possibly implicated in its pathogenesis. The aim of this case report is to alert pediatricians about the occurrence of non-cirrhotic portal hypertension (NCPH) in pediatric patients, in order to avoid the catastrophic consequences of this disease such as bleeding of esophageal varices.

Case description

This case report was approved by the Institutional Review Board of UNIFESP (N. CAAE: 31701414.8.0000.5505) and informed consent forms were signed by patients and their legal guardians.

A preterm male infant, born by cesarean section, with 1,250 g birth weight, 36 cm height and Apgar scores at 1 and 5 minutes of six and eight, was infected by the human immunodeficiency virus (HIV) through vertical transmission. The mother was a user of illicit drugs with irregular use of zidovudine (AZT) during pregnancy and received intrapartum prophylaxis. The child was adopted at 6 months of life. In December 2001 (7 months old) he started follow-up of HIV infection at the Outpatient Clinic of the Discipline of Pediatric Infectious Diseases, UNIFESP/EPM (CEADPE), with HIV viral load of 1,100,000 copies/mL and CD4+ lymphocytes of 819 cells/mm³ (24.1%). He was classified as B2, and was treated with cART (Zidovudine-AZT + didanosine-ddI + Nelfinavir-NFV).

There was good adherence to antiretroviral therapy leading to control of viral replication (undetectable HIV viral load) and normalization of CD4+ T lymphocyte values.
The patient had a history of two hospitalizations at the beginning of follow-up (acute otitis media and pneumonia at 8 months of age and diarrhea two months later), and some uncomplicated clinical conditions, such as chicken pox and scarlet fever during the clinical follow-up. He received the full vaccination schedule recommended for HIV-infected children. cART was maintained until June 2007, when NFV was no longer available, being replaced by Nevirapine (AZT+ddI-nevirapine-NVP). There was control of viral replication and absence of immunosuppression (normal CD4+ levels), with appropriate physical and neurological development, without disease complications or clinical complaints until April 2009, when he started to present with thrombocytopenia (<150,000 platelets/microliter), without bleeding episodes. In March 2013 he started to show immunosuppression (decrease in CD4+ T lymphocyte levels <500 cells/mm³).

In August 2013, aged 13 years, he was clinically stable, weighed 35.6kg, with a body mass index of 14.8 (between the 3rd and the 15th percentiles); 155.5cm tall; H/A=111% (>97th percentile); blood pressure 99×75mmHg; rare posterior inguinal and cervical ganglia (<0.5cm diameter), palpable liver at 3.5cm from the right costal margin and spleen at 6.0cm from the left costal margin (smooth surface, painless). Tanner pubertal stage was G3P3 and neurological examination was normal.

Infectious and oncological causes were investigated and ruled out for the immunosuppression and hepatospleno-megaly: immunity for CMV, hepatitis A and hepatitis B, negative serology for hepatitis C, toxoplasmosis and mononucleosis. The abdominal ultrasound confirmed spleno-megaly; CT of the chest and abdomen showed normal chest, homogeneous hepatospleno-megaly, compressing the kidneys posteriorly, and increased portal vein dimensions (1.8 cm) (Fig. 1).

The myelogram without anomalous cells in the bone marrow disclosed a G/E ratio of 0.9/1; marked erythrocyte hyperplasia with preserved maturation; mild signs of dyserythropoiesis; granulocytic normoplasia with preserved maturation, as well as the presence of mild megaloblasto-

Figure 1 Abdominal computed tomography, showing homogeneous hepatospleno-megaly, exerting posterior compression on the kidneys. São Paulo, SP, Brazil, 2014. The arrows indicate the compression of the kidneys bilaterally by hepatomegaly (R) and splenomegaly (L).

Discussion

Only two other cases of non-cirrhotic portal hypertension (NCPH) have been previously described in children and adolescents infected with HIV: a 10-year-old in Italy9 and a 15-year-old in the United States,10 both with prolonged exposure to ddI and history of esophageal variceal bleeding. No other cases were identified in Brazil. The investigation of this case was triggered because the patient had control of HIV viral replication (undetectable HIV viral load for 12 years), had been using cART with ddI for 12 years without clinical symptoms, had thrombocytopenia, progressive decrease in CD4+ T cell levels and hepatosplenome-galy.

In addition to co-infections by hepatitis B and C virus, the infection of liver cells by HIV may contribute to the progression of liver disease by direct and indirect mecha-nisms.11 The HIV can directly infect hepatocytes, hepatic stellate cells (HSCs) and Kupffer cells. The glycoprotein 120 (gp120) of the HIV bound to the CXCR4 coreceptor can induce apoptosis of hepatocytes and activation of HSCs, both contributing to the formation of liver fibrosis.11 Indirectly, the nucleoside analog reverse transcriptase inhibitors and the HIV itself (effect via peroxisome proliferator-activated receptor - PPAR) can contribute to liver disease by inducing metabolic syndrome. Gastrointestinal tract infection by HIV leads to lipopolysaccharide (LPS) increase, which can stimulate the three types of liver cells to produce proinflammatory cytokines and chemokines that attract activated lymphocytes and monocytes to the liver, further increasing fibrosis.11

One of the clinical presentations of liver disease in HIV mono-infected patient is the non-cirrhotic portal hyperten-sion (NCPH), first described in adults by Maida et al.12
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Parikh et al., in 2014, studying HIV-infected adults with NCPH found that most of them had splenomegaly, thrombocytopenia and elevated alkaline phosphatase. Maida et al., in 2006, assessed a group of 17 HIV-infected adults with cryptogenic liver disease, and comparing them to a control group (HIV-infected patients without liver disease), found prolonged use of ddI as the only independent factor associated with the development of NCPH. The same was observed by Schouten et al. in 2012, demonstrating that the risk factors for the development of NCPH were: long-term exposure (11 years) to ddI alone and/or short-term exposure (4 years) to ddI+ stavudine-D4T or ddI+ tenofovir-TDF combination.

The antiretroviral agents didanosine (ddI), stavudine (d4T) and zalcitabine are stronger inhibitors of mitochondrial DNA polymerase than Zidovudine (AZT), Lamivudine (3TC) and Abacavir (ABC), and cause increased mitochondrial toxicity. Drug-induced depletion of mitochondrial DNA polymerase is an assumed underlying mechanism of lactic acidosis associated with steatosis, steatohepatitis and liver failure in HIV-infected individuals. The association between mitochondrial hepatotoxicity and NCPH was also suggested by Schouten et al. in 2012.

More recently, Parikh et al., in 2014, based on the prevalence of significant factors in patients with NCPH when compared with the control group, proposed a flow chart to assess this diagnosis: exposure to ddI or splenomegaly in an HIV-positive patient without known liver disease should trigger an evaluation for NCPH (excluding patients with a history of alcohol consumption and viral hepatitis detected by serological screening). In the presence of thrombocytopenia, AST>40U/L or AP>115U/L, the patient should be referred to a hepatologist and start the investigation.

Considering that liver involvement can occur for a long period of time before the clinical manifestations of liver disease become evident, and that children infected with HIV by vertical transmission are surviving for longer periods with continuous use of antiretroviral drugs, it is necessary to seek markers capable of identifying liver damage as early as possible.

Siberry et al., in 2014 evaluated the APRI (aspartate aminotransferase/platelet ratio index) as a predictor of liver fibrosis in a cohort of HIV-infected children by vertical transmission in Latin America. The cutoff value for this index in children has not been established, but an index >1.5 seems to be quite specific, although it lacks sensitivity. The studied patient had an APRI of 1.11 at the start of the investigation of hepatosplenic megaly, but this index increased to 2.0 after one month.

The NCPH results in bleeding of esophageal varices. In the study by Parikh et al., 13 of 34 cases with NCPH, 55.9% had bleeding, demonstrating that NCPH is underdiagnosed, perhaps due to lack of an algorithm for the investigation. Esophageal varices were identified in almost 90% of the group with NCPH in this study, a higher prevalence than that found by other researchers: 15% in the study by Mallet et al., in 2007, and 69% in the study by Maida et al., in 2008. The patient we described had small-caliber esophageal varices, without bleeding. The substitution of ddI by another antiretroviral agent in this case aimed to stop the progression of liver fibrosis, decreasing the risk of disease complications.

The purpose of this clinical case report is to alert the professionals that treat individuals infected with HIV/AIDS, particularly pediatricians, about the possibility of NCPH in children and adolescents infected with HIV through vertical transmission submitted to long-term use of cART. One should consider as warning signs the presence of thrombocytopenia and hepatosplenic megaly, regardless of elevated liver enzymes. Liver fibrosis should be investigated in these patients and early identification of the disease can prevent its severe consequences, such as bleeding of esophageal varices.

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Conflicts of interest

The authors declare no conflicts of interest.

References

1. Brasil. Ministério da Saúde. Boletim epidemiológico: HIV-Aids, 2013; 1.
2. Matida LH, Ramos AN Jr, Heukelbach J, Hearst N. Brazilian Study Group on Survival of Children with Aids. Continuing improvement in survival for children with acquired immunodeficiency syndrome in Brazil. Pediatr Infect Dis J. 2009;28:920-2.
3. Belloso WH, Orellana LC, Grinsztejn B, Madero JS, La Rosa A, Veloso VG, et al. Analysis of serious non-AIDS events among HIV-infected adults at Latin American sites. HIV Med. 2010;11:554-64.
4. Rubio A, Monpoux F, Huguon E, Truchi R, Triolo V, Rosenthal-Alleiri MA, et al. Noninvasive procedures to evaluate liver involvement in HIV-1 vertically infected children. J Pediatr Gastroenterol Nutr. 2009;49:599-606.
5. Mallet V, Blanchard P, Verkarre V, Vallet-Pichard A, Fontaine H, Lascaux-Combe C, et al. Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients. AIDS. 2007;21:187-92.
6. Maida I, Garcia-Gasco P, Sotgiu G, Rios MJ, Vispo ME, Martin-Carbonero L, et al. Antiretroviral-associated portal hypertension: a new clinical condition? Prevalence, predictors, and outcome. Antivir Ther. 2008;13:103-7.
7. Cesari M, Schiavini M, Marchetti G, Caramma I, Ortu M, Franzetti F, et al. Noncirrhotic portal hypertension in HIV-infected patients: a case control evaluation and review of the literature. AIDS Patient Care Stds. 2010;24:697-703.
8. Scourfield A, Waters L, Holmes P, Panos G, Randell P, Jackson A, et al. Non-cirrhotic portal hypertension in HIV-infected individuals. Int J STD AIDS. 2011;22:324-8.
9. Giaconnet V, Viganò A, Penagini F, Manfredini V, Maconi G, Camozzi M, et al. Splenomegaly and variceal bleeding in a ten-year-old HIV-infected girl with noncirrhotic portal hypertension. Pediatr Infect Dis J. 2012;31:1059-60.
10. Kochin I, Arnon R, Glasscock A, Kerkar N, Miloh T. Variceal bleeding in an adolescent with HIV diagnosed with hepatoportal sclerosis and nodular regenerative hyperplasia. J Pediatr Gastroenterol Nutr. 2010;50:340-3.
11. Crane M, Iser D, Lewin SR. Human immunodeficiency virus infection and the liver. World J Hepatol. 2012;4:91-8.
12. Maida I, Núñez M, Rios MJ, Martín-Corbonero L, Sotgiu G, Toro C, et al. Severe liver disease associated with prolonged exposure to antiretroviral drugs. J Acquir Immune Defic Syndr. 2006;42:177-82.
13. Parikh ND, Martel-Laferriere V, Kushner T, Childs K, Vachon ML, Dronamraju D, et al. Clinical factors that predict noncirrhotic portal hypertension in HIV-Infected patients: a proposed diagnostic algorithm. J Infect Dis. 2014;209:734-8.
14. Schouten JN, Van der Ende ME, Koëter T, Rossing HH, Komuta M, Verheij J, et al. Risk factors and outcome of HIV-associated idiopathic noncirrhotic portal hypertension. Aliment Pharmacol Ther. 2012;36:875-85.
15. Siberry GK, Cohen RA, Harris DR, Cruz ML, Oliveira R, Peixoto MF, et al. Prevalence and predictors of elevated aspartate aminotransferase-to-platelet ratio index in Latin American perinatally HIV-infected children. Pediatr Infect Dis J. 2014;33:177-82.