

Human immunodeficiency virus type 2 in two Saudi families

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Human immunodeficiency virus type 2 (HIV-2), the second retrovirus that causes the acquired immune deficiency syndrome (AIDS) in humans, is limited in its distribution to West Africa. We report cases in two Saudi families with HIV-2 infection and AIDS, resulting in death of the index cases—the husbands, while the wives and a daughter were maintained on antiretroviral therapy. When HIV viral loads were undetectable in initial assays, further testing confirmed the presence of HIV-2. In the first family, the 30-year-old wife was found to be HIV-positive after the diagnosis in her 30-year-old husband, who later died with AIDS. In the second family, HIV-2 infection was diagnosed in the 50-year-old wife and 18-year-old daughter of a man who had died of AIDS at the age of 48 years. Recognizing HIV-2 infection is essential for appropriate workup, assessment, therapy and care of the pregnant woman.

Human immunodeficiency virus type 2 (HIV-2), the second human retrovirus known to cause the acquired immune deficiency syndrome (AIDS), was first identified in 1987 in West African countries.¹ It remains endemic in certain foci despite the slowly increasing HIV-1 prevalence in these areas.² The prevalence of HIV-2 was reported to range between 10% and 38% in certain locations.^{3,4} The transmission routes are similar to those of HIV-1, with heterosexual and perinatal transmission being the commonest. Compared to HIV-1, HIV-2 was found to spread at a slower rate with lower infectivity in the same population, including high-risk groups.⁵⁻⁸ While progression to AIDS is slower than in HIV-1, survival of HIV-2-infected patients after presenting with AIDS is similar to patients who are HIV-1-infected.⁹ Other variations between HIV-1 and HIV-2 include differences in viral detection assays and response to antiretroviral therapy (ART). Because of the focal epidemiology of HIV-2 and lower prevalence worldwide, the majority of biological and clinical research has been conducted in HIV-1-infected patients.² Very limited data on HIV-2 from areas other than Africa have been reported.¹⁰⁻¹² We are not aware of any case of sexually or perinatally transmitted HIV-2 having been reported from Saudi Arabia or from natives of the WHO

Eastern Mediterranean region. We report cases of HIV-2 infection in two families from Saudi Arabia, including one case of mother-to-child transmission.

CASE 1

A 30-year-old Saudi woman was found to be HIV-positive when she was screened after her husband's diagnosis in 2002. Their two children were HIV-negative. She was asymptomatic, and the baseline CD4+ T-lymphocyte cell count was 400 cells/mm³. The initial HIV viral load was undetectable. HIV screening was done using AxSYM HIV 1/2 gO MEIA (Abbott Laboratories, Abbott Park, IL, USA), CD4+ T-lymphocyte count was done by standard flow cytometry using FACSCalibur (Becton Dickinson, San Jose, CA, USA), and HIV viral load was done using bDNA (Bayer Quantiplex bDNA, Bayer Diagnostics, Walpole, MA, USA). Therapy was initiated in the form of zidovudine, lamivudine and nevirapine when the CD4+ cell count dropped to 300 cells/mm³. The ART course was notable for recurrent and severe adverse effects in the form of nausea, vomiting and diarrhea, forcing discontinuation. The CD4+ cell count continued to decrease, while the HIV viral load remained undetectable. This raised the suspicion of HIV-2 infection, which was confirmed using AxSYM HIV 1/2 gO MEIA (Abbott Laboratories, Abbott

Park, IL, USA) and CHIRON RIBA HIV-1/HIV-2 SIA (Chiron Corp., Emeryville, CA, USA). ART was adjusted several times because of intolerance, and the CD4+ cell count dropped to 110 cells/mm³. She was maintained on trimethoprim-sulfamethoxazole, and eventually tolerated atazanavir and zidovudine-lamivudine combination. At the time of her last clinic visit in July 2009, she had no opportunistic infections and the CD4+ cell count was 233 cells/mm³.

CASE 2

A 30-year-old man (the husband of the patient in Case 1) was diagnosed with AIDS based on a clinical presentation of fever, oral thrush, diarrhea, weight loss and anorexia. HIV screening was done using ELISA (AxSYM HIV 1/2 gO MEIA, Abbott Laboratories, Abbott Park, IL, USA) in 2001. The initial CD4+ T-lymphocyte cell count was 203 cells/mm³. An HIV viral load was not available. The CD4+ count was done by standard flow cytometry using FACSCalibur (Becton Dickinson, San Jose, CA, USA). He was started on ART with a regimen consisting of zidovudine, lamivudine and indinavir, as well as trimethoprim-sulfamethoxazole, in early 2002. The patient was unable to tolerate indinavir, so it was discontinued and replaced by efavirenz, not knowing the patient was HIV-2 positive. Clinical improvement was noted with resolution of the presenting symptoms; however, the CD4+ cell count remained low. HIV viral load was done using bDNA (Bayer Quantiplex bDNA, Bayer Diagnostics, Walpole, MA, USA). All HIV viral load assays revealed undetectable virus. This initially raised the suspicion of a mutant strain, which could not be assessed by the methods used. In 2005, with the patient's CD4+ cell count dropping to 92 cells/mm³, the ART was changed to zidovudine, didanosine and lopinavir/ritonavir. He continued to have recurrent oral thrush with significant weight loss; nevertheless, other opportunistic and granulomatous infections were not found. The patient's HIV viral load had remained undetectable throughout despite a steadily decreasing CD4+ cell count. He died at home in 2005.

CASE 3

An 18-year-old Saudi girl was diagnosed with HIV infection in 2003, when she was 12 years old. She was screened after the death of her father, when her mother was also diagnosed as HIV-positive (Case 4). She had no other risk factors. She has 8 siblings and all were HIV-negative. She was referred to our institution in December 2009. She was asymptomatic, with a CD4+ cell count of 112 cells/mm³ and she was not on therapy. HIV viral load was undetectable. HIV-2 infection

was then suspected and confirmed using AxSYM HIV 1/2 gO MEIA (Abbott Laboratories, Abbott Park, IL, USA) and CHIRON RIBA HIV-1/HIV-2 SIA (Chiron Corp., Emeryville, CA, USA). She was started on treatment with tenofovir-emtricitabine combination, darunavir and ritonavir, along with trimethoprim-sulfamethoxazole.

CASE 4

A 50-year-old woman (the mother of the girl in Case 3) presented to our hospital in May 2009 with symptoms suggestive of AIDS in the form of diarrhea, weight loss and cough. CD4+ cell count was 50 cells/mm³. No opportunistic infection was identified. She was started on lopinavir-ritonavir combination therapy and zidovudine-lamivudine combination therapy, which were changed to tenofovir-emtricitabine and atazanavir because of intolerance. HIV viral load was undetectable, and HIV infection was confirmed as HIV-2, similar to Case 3.

CASE 5

A 48-year-old man died of AIDS complications in 2003 (father of the girl in Case 3 and husband of the woman in Case 4). He was cared for in another facility. Based on information from his wife, he had progressive weight loss and diarrhea despite ART, the details of which were not available. After his diagnosis with HIV/AIDS, his wife was screened and was positive for HIV, but offered no therapy. Only 1 (the girl in Case 3) of their 9 children was confirmed positive. After his death, the wife and the infected daughter did not seek medical care for HIV until the wife presented to our hospital in 2009.

DISCUSSION

Since the early days of discovery, HIV-2 was thought to be different from HIV-1.^{13,14} After the initial report from Africa in 1987,¹ HIV-2 remained focally endemic in western African countries. A few reports indicated that HIV-2 could also be identified in patients in non-African countries. Cases were reported from Europe,^{12,15} with evidence of active transmission within Europe,¹⁶ the USA¹¹ and Japan.¹⁰ There are two reported cases of HIV-2 in the Middle East. The first case from Egypt was of a 40-year-old man from an unnamed Gulf state who was thought to have acquired HIV-2 from a blood transfusion for renal transplantation.¹⁷ The second case from Kuwait was that of a newly arriving Indian man.¹⁸ The patient in the second case is not a native of the region, while the first case was attributed to blood transfusion and without clear mention of the country of origin of the patient. Among 20423 Saudi donors be-

tween 2000 and 2002, none was found to be HIV-1- or HIV-2-positive.¹⁹ Therefore, we consider our cases as the first reported cases of HIV-2 in Saudi Arabia and the WHO Eastern Mediterranean region. We believe the husbands had first acquired the virus from a risky encounter related to a western African infected individual, a means of transmission previously described;¹⁶ then the wives were infected. The travel history of the index patient and the family members indicated that none had traveled outside Saudi Arabia. Our report also documents the first known mother-to-child transmission of HIV-2 in our region.

It is essential to diagnose patients infected with HIV-2 correctly. The implications are important for therapy and prevention. The majority of current serological screening tests are capable of picking up both HIV-1 and HIV-2; however, confirming HIV-2 is limited to certain tests. It is important that treatment providers consider assessment for HIV-2 diagnosis in patients with undetectable HIV RNA and declining CD4+ T-lymphocyte count. Suspicion was raised in our cases because of decreasing CD4+ T-lymphocyte counts with undetectable HIV viral load. Currently, commercial HIV RNA viral load assays cannot detect HIV-2 RNA.²⁰ Subsequently, HIV-2 antiretroviral resistance assays cannot be done. Since most of the tests developed for HIV were done using HIV-1 antigens, there is some degree of cross-reactivity for HIV-2, which could explain the positive testing for HIV-1 initially in our patients. HIV-2 was not confirmed in the husbands, but since we believe that the wives acquired the disease from their husbands, it is almost certain that they had HIV-2.

Heterosexual contact is the commonest mode of

HIV-1 transmission in the Saudi population, constituting the majority of HIV cases in Saudi Arabia, followed by blood transfusion, vertical transmission and intravenous drug abuse.²¹⁻²³ AIDS is still the commonest presentation of HIV in Saudi men, but women are usually diagnosed earlier and they have higher CD4+ T-lymphocyte counts at diagnosis because they are usually diagnosed by screening after diagnosis of their husbands.²²

Data is very limited on the best regimen for treatment of AIDS caused by HIV-2; however, currently available data suggest that regimens containing nucleoside/ nucleotide-reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI) are the best regimens in gaining virological and immunological response. Nevertheless, the activity of PI is still weaker against HIV-2 protease compared to HIV-1 protease.^{24,25} The structure of the building pocket of non-nucleoside-reverse transcriptase inhibitors (NNRTIs) for HIV-2 differs from that of HIV-1, conferring innate resistance to this class of drugs. NNRTIs should not be used for HIV-2.²⁶ Initiation of ART therapy in HIV-2-infected patients should be based on CD4+ T-lymphocyte counts and clinical status. As HIV-2 viral load is undetectable by the currently used assays, even if CD4+ T-lymphocyte counts are extremely low, and it is the viral load that drives disease progression in HIV-2, it may be advisable to start treatment earlier than in HIV-1-positive individuals. CD4+ T-lymphocyte count recovery in treated HIV-2-infected individuals seems to be poor compared to that expected from HIV-1 data, which may justify earlier treatment in HIV-2.²⁷ The need for therapies specific for HIV-2 is pressing and remains un-met.^{28,29}

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