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CLEFT PALATE IN HIV-EXPOSED NEWBORNS OF MOTHERS ON HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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Abstract

Aims—Cleft lip/palate, though rare, is the commonest head and neck congenital malformation. Both genetic and environmental factors have been implicated in the aetiopathogenesis but the role of *in-utero* exposure to human immunodeficiency virus (HIV) and highly active antiretroviral therapy (HAART) is still being investigated. This short communication reports the occurrence of cleft palate in three newborns exposed *in-utero* to HIV and HAART.

Material and methods—This is a case series of HIV-exposed newborns observed to have cleft palate among a larger cohort of HIV-exposed and unexposed newborns in a study evaluating the effect of HIV infection and HAART on newborn hearing. The Risk Ratio (RR) was calculated to detect a potential association between *in-utero* exposure to Efavirenz containing ART and cleft palate.

Results—Three HIV-exposed newborns with cleft palate were identified during hearing screening performed on 126 HIV-exposed and 121 HIV unexposed newborns. Two had exposure to tenofovir+lamivudine+efavirenz (TDF+3TC+EFV) while the third had exposure to zidovudine +lamivudine+nevirapine (ZDV+3TC+NVP) during the first trimester. There was no statistically

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significant association between presence of cleft palate and exposure to an EFV containing HAART regimen (p=0.07, RR=10.95 [0.94-126.84]).

Conclusions—This communication highlights the possible aetiologic role of HAART in cleft palate, the need for further prospective follow-up studies and establishment of antiretroviral pregnancy, birth and neonatal registries.

Keywords

Cleft palate; efavirenz; highly active antiretroviral therapy (HAART); human immunodeficiency virus (HIV); nevirapine; newborns

INTRODUCTION

Highly active antiretroviral therapy (HAART) is effective in delaying maternal human immunodeficiency virus-type 1 (HIV-1) disease progression, prevention of mother-to-child transmission (PMTCT) of HIV-1 and reduction of HIV-related infant death.[1,2] The World Health Organization (WHO) consolidated 2013 HIV guidelines have simplified antiretroviral therapy (ART) regimens by the introduction of an inexpensive fixed-dose combination utilizing tenofovir disoproxil fumarate, lamivudine/emtricitabine and efavirenz (TDF+3TC/FTC+EFV).[3] Efavirenz (EFV) is therefore recommended to be taken in combination with two other nucleos(t)ide reverse transcriptase inhibitors (NRTIs) as a first line ART regimen [4,5] while nevirapine containing combination therapy is another first line ART regimen recommended when EFV is not available or is contraindicated. A teratogenic effect of EFV in an animal model has been reported to cause neural tube defect [6] and there are also case reports of birth defects in human newborns exposed *in-utero* to EFV in the first trimester of pregnancy.[7,8,9] However, available literature on the potential association of HAART and cleft palate has not been conclusive perhaps because of the confounding effects of genetics and environment in the development of cleft lip/palate.[10,11]

This short communication describes three cases of cleft palate in HIV-exposed newborns born to mothers on HAART. It is hoped that this communication will add to the pool of information on the possible association between HAART and cleft lip/palate and encourage further pregnancy outcome and birth defect surveillance in the at risk populations.

MATERIAL AND METHODS

This is a case series of HIV-exposed newborns observed to have cleft palate among newborns who underwent hearing screening with Auditory Brainstem Responses (ABR) at the Department of Otorhinolaryngology, University College Hospital, Ibadan, Nigeria. They were part of a larger cohort of HIV-exposed and unexposed newborns in a study of the effect of HIV infection and HAART on newborn hearing approved by the Joint University of Ibadan/ University College Hospital, Ibadan Institutional Review Committee. The mothers gave informed consent for their newborns to participate in the study. Consecutive babies were recruited in both groups on days of study from the APIN/PEPFAR PMTCT program. It is the policy of the APIN/PEPFAR PMTCT program that all HIV-exposed babies receive NVP for 6 weeks from birth and have HIV DNA PCR at 6 weeks and 3

months to evaluate for PMTCT of HIV infection. Their mothers were managed on HAART regimens at the APIN/PEPFAR clinic in Ibadan. As recommended by the National policy on Intermittent Preventive Therapy for Malaria in Pregnancy, mothers also received three doses of sulfadoxinepyrimethamine in the second and third trimesters of pregnancy. The Risk Ratio (RR) was calculated to detect a potential association between *in-utero* exposure to Efavirenz containing ART as well as Nevirapine containing ART in the HIV-exposed newborns and cleft palate. Level of significance was determined at $p < 0.05$, at 95% Confidence Interval (CI).

RESULTS

One hundred and twenty six (126) HIV-exposed and 121 unexposed who served as the controls were screened for hearing loss by ABR. Three of the 126 HIV-exposed newborns were found to have cleft, their history is described below. None of the 121 HIV-unexposed was found with cleft anomalies. There was no statistically significant association between presence of cleft palate and exposure to an EFV containing HAART regimen (p=0.07, RR=10.95 [0.94-126.84]) or exposure to a NVP containing HAART regimen (p=0.1769, RR=0.18 [0.02-1.97]).

Case I

A 37-week gestation newborn was delivered to a 32-year-old HIV-infected mother. The mother of the baby was diagnosed with HIV infection 15 months prior to the index baby delivery with a CD4+ T lymphocyte count of 142 cells/mm^3 and plasma HIV-1 RNA of 271,841copies/ml. Her last CD4+ T lymphocyte count two months before delivery was 171cells/mm^3. She had become pregnant 6 months after commencing TDF+3TC+EFV and the HAART regimen was changed to ZDV+3TC+NVP at two months gestation. Mothers also received trimethoprim-pyrimethamine in the first trimester of pregnancy on account of CD4 cell count of <200 cells/mm^3. The mother also ingested herbal medication to treat fever during pregnancy. She delivered a female baby with a birth weight of 2.8kg and length of 47.9cm. During the baby's hearing evaluation with Auditory Brainstem Response (ABR), an incomplete unilateral cleft of the primary palate was observed and no other congenital malformation. There was no family history of congenital malformation. The baby tested negative for HIV infection and her CD4+ T lymphocyte count was 1596 and percentage was 49.4% at birth. The ABR hearing screening showed that there was no hearing impairment.

Case II

A 36-week gestation female newborn with a birth weight of 3.0kg and length of 47.6cm was delivered to a 38-year-old HIV-infected mother. The mother had been diagnosed with HIV, 60 months prior to index delivery. During the first trimester, CD4+ T lymphocyte count was 201 cells/mm^3 and HIV-1 RNA was 380 copies/ml. Her last CD4+ T lymphocyte count before delivery was 218 cells/mm^3. She was receiving ZDV+3TC+NVP before, during and after pregnancy. During the clinical examination and the baby's hearing ABR evaluation a unilateral incomplete secondary cleft palate was observed with no other congenital malformation. The baby tested negative for HIV DNA PCR and her CD4+ T lymphocyte

count was 1714 and CD4% was 22.4%. The ABR hearing screening showed that there was bilateral hearing impairment.

Case III

A 36-week gestation newborn was delivered to a 35-year-old mother who was diagnosed with HIV 80 months prior to delivery. CD4+ T lymphocyte count during the first trimester was 414 cells/mm^3 and HIV-1 RNA was 231 copies/ml. Her last CD4+ T lymphocyte count before delivery was 435 cells/mm^3. When she became pregnant, she informed her physician who changed her antiretroviral medication from TDF+3TC+EFV, to TDF+3TC+NVP during the first trimester. The mother had a history of herbal medication ingestion for treatment. She eventually gave birth to a male baby with a birth weight of 2.8kg and length 47.4cm. During examination and the baby's hearing ABR evaluation, a cleft of the primary and secondary palate was observed without any other malformation. He is the third child in the family where there is no other family history of congenital malformation. The child's CD4+ T lymphocyte count was 1250 cells/mm^3 and percentage was 20.2%. The ABR hearing screening showed that there was impairment of hearing bilaterally.

DISCUSSION

This is the first case series of cleft palate in newborns that had intrauterine exposure to HIV and HAART regimens in sub-Sahara Africa. Although there is no formal registry documenting the extent of congenital malformations in Nigeria and probably in sub-Saharan Africa, a study in Nigeria reported prevalence rate of orofacial cleft to be 0.5 per 1000 population [12] while another similar study in Ghana reported an incidence of orofacial cleft to be 1.31 per 1000 live birth.[13] These studies however did not evaluate a possible association between orofacial cleft and HIV as well as HAART exposure. Orofacial clefts are caused by primary defects in the fusion of craniofacial processes in the first trimesters of intra-uterine life. The aetiologic factors in orofacial clefting are multifactorial and both genetic and environmental factors have been implicated.[14,15] In Nigeria, a missense mutation A34G in the MSX1 gene has been reported to play a role in the etiology of cleft lip/palate.[16] EFV used during first trimester in pregnancy[17] and folic acid deficiency[18,19] have also been associated with the development of orofacial cleft.

The National Institute of Child Health and Human Development (NICHD) International Site Development Initiative (NISDI) Perinatal Study Group report from South America reported only one case of cleft palate from babies of 249 pregnant women who used anti-retroviral medications during pregnancy.[20] The teratogenic role of EFV in the congenital development of orofacial cleft and neural tube defect has continued to receive the interest and attention of clinicians and researchers.[7-11,17,21-23] In the present study, HAART was administered to the mothers of the three HIV-exposed newborns with cleft palate prior to the index pregnancy to delay HIV disease progression. Two of the three HIV-exposed newborns with cleft palate had *in-utero* exposure to the TDF+3TC+EFV regimen while the third baby had exposure to maternal ZDV+3TC+NVP regimen. EFV is an effective drug against HIV/AIDS but the major medical concern is its safety in pregnancy.[8,9] Because birth defects have been reportedly higher in newborns exposed to EFV during the first

trimester, it is contraindicated in pregnant women during the first trimester and in women who have a high likelihood of becoming pregnant.[17,21] Two babies in this report were exposed to EFV *in-utero* during the first trimester. This present study also showed that there is a ten-fold increase in the risk of developing cleft lip/palate in newborns exposed to EFV more than the unexposed although the difference was not statistically significant, there was a noted trend for the association (p=0.07, RR=10.95 [0.94-126.84]). This is a striking finding since the antiretroviral pregnancy registry interim report issued in 2011 did not find any increase in birth defects in newborns exposed to EFV in the first trimester compared with second/third trimester.[24] Studies have not shown a link between congenital orofacial cleft and TDF+3TC use.[18] The association between NVP and cleft lip/palate has been rarely mentioned in the literature.[8] The single newborn with *in-utero* exposure to NVP in this study may be due to chance alone.

Potential mothers on ARVs are normally counseled on pregnancy but the mothers of these babies with orofacial cleft claimed ignorance of their pregnancy and therefore continued exposure to HAART drugs. The few numbers of HIV-exposed newborns with cleft palate in this study does not permit any definitive conclusions to be made on the teratogenicity or safety of the antiretroviral medications vis-à-vis efavirenz and nevirapine.

These HIV-infected mothers also ingested other potentially teratogenic drugs in pregnancy including trimethoprim-pyrimethamine and sulfadoxine-pyrimethamine, which are folate antagonists. These anti-folates have been linked to development of cleft palate.[25] They are usually administered late in second and early third trimester and therefore may not be implicated in the development of cleft palate in the three newborns. Excess intake of Vitamin A and deficiency of folic acid during first trimester of pregnancy has been linked to development of congenital anomalies like cleft lip/palate.[26,27] The mothers of these newborns belong to the low socioeconomic class and consumption of low nutrient food deficient in folic acid due to overcooking may also have contributed to the development of cleft lip/palate. The herbal medication used by two of these mothers during pregnancy to treat fever may have also played a role in the aetiopathogenesis of cleft palate.[26,28] However, it is not known whether the herbal medication contained a teratogenic substance. Use of herbs during pregnancy should be discouraged especially during the first trimester.

In conclusion, although EFV containing antiretroviral regimen has been shown to be effective even in advanced HIV - 1 disease,[29,30] however it must be used with caution during the first trimester when the teratogenic side effect of EFV is high. The aetiology of cleft palate in these three HIV-exposed newborns is uncertain because of multiple suspected factors, which they were exposed to *in-utero*. The teratogenic roles of HAART and HIV to which these babies were exposed in utero needs further review. This communication highlights the need for further prospective follow-up studies and establishment of antiretroviral pregnancy, birth and neonatal registries especially in Nigeria.

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CLINICAL RELEVANCE

Scientific rationale for the study: Many factors have been implicated in the aetiology of orofacial clefting but the role of HAART used by HIV infected mothers is still being investigated. There are reports that Efavirenz caused birth defects in animal models but controversy still exists on its causative role in orofacial clefting in newborns who are exposed inutero to it. The available literature is insufficient to reach any conclusion.

Principal findings: This study presents three HIV-exposed newborns with cleft palate whose mothers were on HAART.

Practical implication: This adds to the existing knowledge and cautions antiretroviral medication use during early pregnancy.