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Severe HIV disease in neonates- report of six cases

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Summary

Among infants with maternally transmitted human immunodeficiency virus (HIV) infection there may be rapid progression of disease especially when infected at an early stage of development, resulting in the onset of severe immunodeficiency and clinical disease soon after birth. This is a case report of six neonates who fulfilled the WHO criteria for presumptive diagnosis of severe HIV disease based on the presence of some clinical signs and symptoms. Cases 1 and 6 had severe wasting and severe sepsis, case 2 had severe wasting, oral thrush and severe sepsis, case 3 had severe pneumonia, oral thrush and severe sepsis, case 4 had severe pneumonia and severe sepsis, while case 5 had severe wasting and oropharyngeal thrush. DNA polymerase chain reaction (PCR) was positive in cases 5 and 6. Where HIV virologic studies are largely unavailable, clinical and immunologic criteria can be used for a presumptive diagnosis of severe HIV infection in children younger than 18 months.

Keywords: *Severe HIV disease, neonates, presumptive diagnosis.*

Résumé

Parmis les enfants atteints de l'infection du Virus Immunodéficience Humaine (VIH) transmis maternellement, il peut avoir progression rapide de la maladie surtout quant l'on est infecte en debut de developpement, resultant d'une immunodeficience severe et bientot d'une maladie clinique apres la naissance. Ceci est un cas rapporte de 6 nouveau nees qui ont remplis les criteres de l'OMS pour le diagnostique presumptif du VIH severe base sur la presence de certains signes cliniques et symptomes. Les cas 1 et 6 avaient une perte sévère et une septicémie grave, le cas 2 avait une perte sévere, les aphtes, et une septicémie grave, le cas 3 avait une pneumonie sévere, les aphtes et une septicémie grave, le cas 4 avait une pneumonie sévere et une septicemie grave, alors que le cas 5 avait une perte sévere.. La réaction chaine polymérase (PCR) d'ADN était positif chez les cas 5 et 6. Ou les examens virologiques de VIH sont largement indisponibles, les critères cliniques et immunologiques peuvent etre utilisés pour les diagnostiques présomptifs de l'infection de VIH sévere sur les enfants de moins de 18 ans

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Introduction

Infants with perinatally acquired human immunodeficiency virus (HIV) infection have widely variable courses. In about a fifth of these infants there is a rapid progression to profound immunodeficiency and severe clinical disease soon after birth [1,2]. Where age-appropriate HIV-detection tests (i.e., HIV culture, HIV polymerase chain reaction (PCR), or HIV p24 antigen) are unavailable, WHO recommends that a presumptive diagnosis of severe HIV infection can be made in infants younger than 18 months if the infant is confirmed to be HIV antibody positive and is symptomatic with 2 or more of the following: oral thrush, severe pneumonia, severe wasting/malnutrition and severe sepsis [3]. We present six neonates who fulfilled the WHO criteria for severe HIV disease based on clinical and immunologic criteria.

Case reports

There were six neonates made up of 4 males and 2 females. All were delivered at term except for case 3 who was delivered at 36 weeks gestation. The general characteristics of the neonates are shown in Table 1. The clinical features and the outcome of the six neonates are presented in Table 2. Cases 1 and 6 had severe wasting and severe sepsis, case 2 had severe wasting, oral thrush and severe sepsis, case 3 had severe pneumonia, oral thrush and severe sepsis, case 4 had severe pneumonia and severe sepsis, while case 5 had severe wasting and oropharyngeal thrush.

All the babies and the mothers tested seropositve to HIV-1. The HIV status of the fathers of cases 1 and 2, were unknown as they declined screening, whereas in cases 3, 5 and 6, the fathers were sero-negative and in case 4, the father was sero-positive. In cases 3 and 5, the mothers were commenced on highly active antiretroviral therapy (HAART) from the third trimester (at booking) of

Table 1: The general characteristics of the six neonates

Patient	Sex	GA at birth	Mode of delivery	Birth weight	Age at presentation	Weight at presentation
1.	M	38 wks	SVD	3.8kg	28days	2.4kg
2.	F	40wks	SVD	3.4kg	13days	2.1kg
3.	M	36wks	EMCS	2.4kg	At birth	2.0kg (at 6days)
4.	F	40wks	SVD	Not known	23days	2.8kg
5.	M	38wks	ELCS	2.5kg	27days	2.5kg
6.	M	38wks	SVD	2.7kg	21days	2.0kg

(EMCS = emergency caesearean section; ELCS = elective caesearean section; GA = gestational age; SVD = spontaneous vaginal delivery).

Table 2: The clinical features, and the WHO paediatric clinical staging of the six neonates

Patient	Clinical presentation	WHO clinical staging[3]	Outcome
1.	Progressive weight loss, fever, cough bilateral leg swelling, generalized body rash, normal BP	presumptive Stage 4	DAMA
2.	Weight loss, fever, diarrhoea, generalized lymphnode enlargement (GLNE), oral thrush, hepatomegaly	presumptive Stage 4	DAMA
3.	Respiratory distress, oral thrush, fever, seizure, GLNE, hepatomegaly, splenomegaly, hypertonia	presumptive Stage 4	Died at 4½ months of age
4.	Deep ulcers, GLNE, respiratory distress dermatitis, hepatomegaly, ear discharge	presumptive Stage 4	Died at 25 days of age
5.	Fever, poor weight gain, vomiting, oro-pharyngeal thrush, GLNE	presumptive Stage 4	On follow up
6.	Weight loss, seizure, fever, hepatomegaly hypertonia, microcephaly	presumptive Stage 4	Died at 42 days

(DAMA = discharged against medical advice; BP = blood pressure; GLNE = generalized lymph node enlargement)

Table 3: The results of the investigations of the six neonates

Patient	FBC	Blood culture	CSF culture	SEUCr	CD4 count	Others
1	Normal	*Klebsiella sp*	not done	Normal	340	proteinuria
2	Leucocytosis	*Klebsiella sp.*	Not done	Normal	620	None
3	Normal	*Klebsiella sp.*	*Klebsiella sp*	Normal	200	bilateral perihilar opacities on chest radiograph
4	Leucopenia	*Staph aureus*	Not done	Not done	170	culture of ear swab yielded *Staph aureus*
5	Anemia	No growth	No growth	Normal	231	DNA PCR positive
6	Leucocytosis	*Klebsiella sp.*	*Klebsiella sp*	Normal	251	DNA PCR positive

(FBC = full blood count; SEUCr = serum electrolyte urea and creatinine; CSF = cerebrospinal fluid; PCR = polymerase chain reaction)

pregnancy because of their low CD4+ count (of 160 cells/mm^3 and 120 cells/mm^3 respectively). At birth, case 3 received single dose nevirapine (which was the antiretroviral prophylaxis at that time) while case 5 received single dose nevirapine and six weeks of zidovudine. In case 4, the mother was symptomatic with chronic cough, severe weight loss, generalized lymphadenopathy and dermatitis but was not on therapy. The other mothers were not screened in pregnancy. DNA PCR using the dried blood spot (DBS) method became available in our institution from November 2007 and was done in only cases 5 and 6 and they were both positive. Table 3 shows the results of the investigations done. Cases 3, 5 and 6 were commenced on antiretroviral therapy with syrup zidovudine, nevirapine and lamivudine. Both cases 3 and 6 have died and only case 5 is still being followed up and at 4 months, he weighed 6.5kg.

Discussion

Among infants with vertically transmitted HIV infection, there are three patterns of disease progression (rapid progressors, slow progressors and long term survivors)[1,2]. The rate of disease progression varies directly with the severity of the disease in the mother and on whether the fetus was infected at an early stage of development [2]. In the majority, the disease progresses much more slowly. In 15-20% of cases however, there is a rapid progression to profound immunodeficiency [1,2,4].

The risk that the early and severe form of disease will develop is higher in newborn infants whose mothers have advanced disease and a high viral load, such that the fetuses are infected at an early stage of development with early peak of viremia and depressed CD4 percent resulting in the onset of clinical disease soon after birth [2]. This appears to have been the case in these six neonates. High maternal viral load (as determined by high plasma levels of HIV-RNA, low CD4+ cell count and advanced clinical HIV disease) during pregnancy could result in, not only an early transmission in utero but also transmission of a larger viral inoculum and thus predicts the risk of disease progression in these infants[2,5]. In the mothers of cases 3, 4 and 5, although viral RNA copies and p24 antigen levels were not done, a high viral load could be inferred from the very low CD4+ count in the mothers of cases 3 and 5 and the presence of AIDS-defining symptoms in the mother of case 4.

It has been suggested that, if intrauterine infection coincides with the period of rapid proliferation of CD4+ cells in the fetus, majority of the immunocompetent cells in the fetus will be infected [1]. Following normal migration of these cells to the marrow, spleen, and thymus, there is systemic delivery of HIV which is not controlled by the immature immune system of the fetus. Thus, widespread infection would be established before the normal development of the immune system, causing more severe impairment of immunity [1]. Rapidly progressive AIDS in newborns therefore correlates with an absence of HIV-1-specific humoral [6] and cellular (diminished cytotoxic T lymphocytes) [7] immunity and immune tolerance [8] (where antigens present in the fetal thymus during early development of the organ are regarded as self-antigens, and the naive immune system learns not to respond against them). Papiernik *et al*[4] also identified the occurrence of thymic abnormalities in fetuses of HIV-infected women which suggests an interaction between the virus and the fetal immune system and which may account for the early and severe immune deficiency observed in 15 to 20 percent of cases.

Virtually all HIV-exposed children are HIV-antibody positive at birth, although only 15%-30% may be actually infected [9]. Virologic studies using polymerase chain reaction (PCR) [10,11], viral culture and p24-antigen assay [11,12] are the most sensitive and specific assays for detecting infection in HIV-exposed children. These parameters, if positive at birth, reflects infection in utero [11]. These tests are however very expensive and not readily available in resource-poor settings. DNA PCR using the dried blood spot (DBS) method only became available in our institution from November 2007. When these virologic studies are not available, a presumptive diagnosis of severe HIV disease can be made in infants younger than 18 months if the infant is confirmed to be HIV antibody positive and is symptomatic with 2 or more of the following: oral thrush, severe pneumonia, severe wasting/ malnutrition and severe sepsis [3]. All the babies were HIV-1 antibody positive and each of them had at least two of the diagnostic criteria. The DNA PCR results of two of the cases were positive further lending support that these clinical signs and symptoms may assist in early diagnosis of HIV infection in young infants where virological testing is not available and may guide the decision to initiate antiretroviral drugs.

CD4+ T-lymphocyte depletion is a major consequence of HIV infection and is responsible for many of the severe manifestations of HIV infection. Low age-specific CD4+ counts thus correlates with immunosuppression in children and is useful for describing the immunologic status of HIV-infected

children [9,13]. Rich [14] identified a low maternal CD4 count and infant CD4 percent as characteristics associated with rapid progression to CDC Category C disease or death by 6 months of age. The CD4 lymphocyte count of all the babies and that of the mothers of cases 3 and 5 were in the severe immune suppression range.

Presence of lymphadenopathy, hepatomegaly, or splenomegaly in HIV-exposed infants in the neonatal period have also been described as early infant characteristics of disease progression[1,11,14-16]. The first 2 signs were seen in all the babies except case 1, whereas splenomegaly was seen in case 3. Ledesma-lujan [17] also described a case of AIDS in a neonate whose clinical symptoms included poor growth, hepato-splenomegaly and recurrent infections.

Although programmes to prevent mother-to-child-transmission (MTCT) have been shown to be feasible, acceptable and cost-effective [5,18], interventions to reduce MTCT have not yet been implemented on a wide scale in resource-constrained settings. Uptake of pregnant women testing is still very low in developing countries [19]. Only 2 of the mothers had interventions to reduce MTCT and even at that, the interventions were started late.

Conclusion

A presumptive diagnosis of severe HIV disease can be made in infants less than 18 months using a combination of certain symptoms and signs, especially in places where infection cannot be confirmed by virologic studies.

Recommendation

Renewed efforts are urgently required to offer HIV counselling and testing to pregnant women as standard practice in antenatal care (or in labour). Also, HIV-infected pregnant women should be started on antiretroviral drugs for treatment of their disease or for prophylaxis at the right time in order to decrease the viral load in the mother and reduce the risk of early transmission to the fetus.

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