Maternal transmission of SIV_{smm} in rhesus macaques

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Fifteen SIV-infected rhesus monkeys delivered 13 livebirths and two stillbirths; one livebirth died at three days of age. While all infants were culture-negative for SIV at birth, nine had maternal antibodies that disappeared by six months of age. Three infants subsequently seroconverted and became virus positive at 9–15 months. Milk samples from all mothers were virus-negative at parturition but samples from four animals were virus-positive at nine and 12 months. This study documents maternal transmission of SIV and suggests transmission by breast-feeding.

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Introduction

HIV infection and AIDS are becoming an increasingly important problem in children born to HIV-1-infected mothers [1,4,5,14,22], with rates of mother-to-child transmission of HIV-1 ranging from 24% in asymptomatic mothers to 65% in mothers who have previously given birth to an HIV-infected infant [2,5,9,23,24]. Due to the increasing magnitude of pediatric HIV infection, the difficulties associated with diagnosis in infants, and the need for early diagnosis in order to initiate appropriate therapy (or prevent treatment with potentially toxic drugs in seropositive but noninfected infants), additional studies are needed to 1) determine more precisely the timing of infection, 2) evaluate maternal factors that may increase or decrease the potential for transfer of infection to offspring, 3) develop better diagnostic methods to allow rapid and precise diagnosis of HIV infection in infants, 4) evaluate pharmacologic or immunologic treatments for the prevention of mother-to-infant transmission, and 5) evaluate therapeutic regimens early in the course of infection in neonates.

Based on the close genetic, antigenic, and biologic relationship between HIV and some simian immunodeficiency viruses (SIV) [3,8,13,16], the SIV-infected macaque should prove to be an excellent model system to evaluate the various parameters associated with perinatal/postnatal infection with an AIDS-like lentivirus. In this report, we present preliminary observations from a study designed to evaluate the perinatal/postnatal transmission of SIV_{smm} in experimentally infected rhesus macaques, and to determine the feasibility of using experimentally infected rhesus macaques as a model system for the study of perinatal HIV infection.

Materials and methods

Fifteen adult, timed-mated, female rhesus monkeys were divided into three groups of five animals and exposed to SIV_{smm} during early (day 28–35), mid- (day 71–78), and late (day 146–150) gestation. Timed mating was carried out as described [20], and each pregnant female was exposed to virus by intravenous, intramuscular, and intravaginal inoculation of approximately 1×10^4 $TCID_{50}$ at each site. The virus strain used in these studies, SIV_{smm9}, was obtained from naturally infected mangabeys [7]

and has been shown to infect rhesus macaques and to induce a high incidence of an AIDS-like disease [19]. To confirm infection, all virus-exposed females in the early and mid-gestation groups were screened at three and six weeks after inoculation serologically by EIA (HIV-2 EIA kit, Genetics Systems) and by cocultivation of peripheral blood mononuclear cells (PBMC) with normal human PBMC in attempts to isolate SIV. Cultures of PBMC and serologic evaluations were done on the females in the late gestation group within a week after parturition.

All pregnant females were allowed to go to term and deliver naturally; each infant remained with its mother for at least 12 months. Each mother and liveborn infant were evaluated within a week of delivery and at quarterly intervals thereafter by serology and coculture of PBMC; a milk sample was also collected from the mother at each examination and tested for the presence of virus. Milk (2 to 4 ml) was collected following IV administration of 2–3 units of oxytocin to the mother [18]; these samples were centrifuged at 1,500 rpm for 15 minutes to pellet cells present in the milk. Following centrifugation, the milk fraction beneath the lipid layer was removed and cocultured with PHA-stimulated human PBMC; the pelleted cell fraction was resuspended in medium (RPMI-1640 containing glutamine, 10% fetal bovine serum, and interleukin 2) and cultured similarly. Gentamicin was added to all cultures at a concentration of 100 μg/ml. Cocultures were maintained six weeks before being discarded as negative.

Due to the limited amount of blood that can be collected from infant rhesus monkeys, pokeweed mitogen (PWM) assays and PCR determinations were not done until the infants were 5–12 months of age. The PWM assays were done as previously reported [15]. The PCR amplifications were done according to established techniques [27] using two sets of amplimers and probes specific for the *gag* region of SIV_{smm}.

Results

Offspring delivered by 15 experimentally infected macaques included two stillbirths (at 95 and 117 days postinfection of the mother) and 13 livebirths; one liveborn infant died at three days of age. Cultures of multiple tissues from the stillbirths and neonatal death were negative for virus, and histologic evaluation of tissue sections from these three animals did not reveal any specific changes suggestive of a retrovirus infection.

All 15 inoculated adult females seroconverted by three to six weeks postexposure, and virus was isolated from PBMC of 14 of the 15 animals at three weeks postexposure; 12 of the 15 animals had PBMC that were positive for virus at parturition (Table I). PBMC cultures for six of 15 females were consistently virus-positive throughout a 12-month postpartum follow-up, while cultures for three animals were intermittently virus-positive during this period. Cultures from five animals were virus-negative between three weeks postinfection and six months postpartum. Cultures for one animal remained virus-negative throughout the study period. Milk samples from four of 12 females tested were virus-positive between nine and 12 months postpartum.

Two of the experimentally infected females (animals RTw and RTu) died of an AIDS-like disease at 11 and 13 months postpartum. A third animal (OPE-258) died 19 months postpartum from causes not apparently related to the SIV infection. Four additional females showed clinical AIDS-like disease (14–22 months postinfection), characterized by chronic diarrhea and weight loss (24–41%), decreased numbers of $CD4^+$ cells, decreased $CD4^+/CD8^+$ cell ratios, lymphadenopathy, and elevated IgG values (2,860 to 4,620 mg/dl).

Animal RTw, infected with SIV_{smm} in early gestation, died 15 months postinfection (11 months postpartum) following an extended clinical disease characterized by chronic diarrhea and weight loss (42%), generalized lymphadenopathy, *Campylobacter* infection (blood and colon), elevated IgG values (3,623 mg/dl), gastric lymphoma and ulceration and immunosuppression ($CD4^+$ cell count of 520 and $CD4^+/CD8^+$ cell ratio of 0.49). Virus was consistently isolated from PBMC of this animal throughout the 15-month postinfection period and she developed high EIA titers. Multiple milk samples collected from this animal, and PBMC from her infant, were culture-negative for SIV_{smm}.

Animal RTu, infected with SIV_{smm} in mid-gestation, died 17 months postinfection (13 months postpartum) following a clinical illness characterized by chronic diarrhea and weight loss (30%), splenomegaly (31.3 grams), generalized lymphadenopathy, anemia, and immunosuppression ($CD4^+$ cell count of 220 and $CD4^+/CD8^+$ cell ratio of 0.41). Cultures of PBMC from this animal were consistently virus-positive and she also developed high EIA titers. Milk samples collected at nine and 12 months postpartum were virus-positive. Her offspring seroconverted and had a virus-positive coculture of PBMC at nine months of age.

PBMC cultures for all infants were virus-negative at time of birth (Table II). All infants in the early and mid-gestation groups and one infant in the late gestation group had low levels of maternal antibodies to SIV_{smm}. Maternal antibodies had decreased to undetectable levels prior to three months

TABLE I. Virus isolation: Maternal SIV transmission study[1]

Animal number	Time postinoculation		At time of parturition	Time postpartum				
	3 weeks	6 weeks		3 mo.	6 mo.	9 mo.	12 mo.	15 mo.
Group 1[2]								
RYS[8]	+	+	+	+	+	–	+	+
OPE-196	+	+	+	+	–	–	–	–
RTw	+	+	+	+	+	+[5]		
CF-50	+	+	+	–	–	–	–	+
OPE-258	+	–	–	–	–	–	–	–[6]
Group 2[3]								
RUp	+	+	+	+	+	+	+	
OPE-218[9]	+	–	–	–	–	–	–	
5618[9]	+	+	+	+	–	+	+	
RTu[10]	+	+	+	+	+	+	+[7]	
OPE-168	+	+	+	+	+	–	–	
Group 3[4]								
N-790	ND	ND	+	+	+	+	ND	
103T[10]	ND	ND	+	+	+	+	+	
083Z	ND	ND	+	–	–	–	–	
N-645	ND	ND	+	+	+	+	ND	
097T	ND	ND	–	–	–	–	ND	

[1]All animals seroconverted.
[2]Group 1 animals inoculated between day 28–35 of gestation.
[3]Group 2 animals inoculated between day 71–78 of gestation.
[4]Group 3 animals inoculated between day 146–150 of gestation.
[5]Died at 15 months postinfection (11 months postpartum).
[6]Died at 23 months postinfection (19 months postpartum).
[7]Died at 17 months postinfection (13 months postpartum).
[8]Animal's infant is virus-positive.
[9]Milk sample virus-positive.
[10]Milk sample and PBMC from the infant are virus-positive.
ND, not done.

of age in four of these nine infants, and between three and six months in the other five infants. Three infants subsequently seroconverted with virus-positive cultures of PBMC at nine, 12, and 15 months of age. The mothers of two of the virus-positive infants had virus-positive milk samples. The infants of two additional females with virus-positive milk samples have remained seronegative and virus-negative throughout a 12-month follow-up. One virus-positive infant, RDs-2 (mother RTu), developed progressive clinical disease and died at 16 months of age (seven months after it seroconverted and became virus-positive). Observations for this infant included diarrhea and weight loss, long standing anemia, generalized lymphadenopathy, thymic atrophy, focal pneumonia, terminal lymphopenia, and immunosuppression ($CD4^+$ cell count of 480 and $CD4^+/CD8^+$ cell ratio of 0.69). The characteristics of the anemia in this infant are presented in another report in this issue [12]. The other two virus-positive infants in this cohort are showing progressive disease characterized by lymphadenopathy, decreasing numbers of CD^+ cells (810 and 860), and elevated IgG values (2,082 and 3,112 mg/dl).

The results of preliminary PWM assays and PCR detection of SIV *gag* sequences in PBMC from these 12 infants are summarized in Table III. These data suggest that as many as 10 of the 12 infants were SIV-infected, or have been exposed to noninfectious SIV antigenic material.

Discussion

The results presented here demonstrate maternal-to-infant transmission of SIV_{smm} following experimental infection of macaques. Based on conventional serology (EIA) and virus isolation from PBMC, three of 12 (25%) rhesus macaque infants born to SIV-infected mothers were SIV-infected. However, the infants did not seroconvert or have detectable virus until they were nine, 12 and 15 months of age, suggesting that virus infection most likely occurred as the result of consumption of virus-containing milk. This report represents the first documentation of maternal–infant transmission in the SIV-infected macaque model. A previous study failed to demonstrate infection in eight rhesus monkey infants delivered by C-section, and two abortuses, from mothers experimentally infected with SIV_{Delta} [6]. These observations are in contrast to studies of the maternal–infant transmissi n of

TABLE II. Infant EIA titers[1]: Maternal SIV transmission study

Infant[2]	Birth	3 months	6 months	9 months	12 months	15 months
Group 1[3]						
RWq-2	12,800	800	0[4]	0	3,200	102,400[5]
RUg-2	800	0	0	0	0	0
RTq-2	12,800	800	0	0	0	0
RLr-2	6,400	400	0	0	0	0
REq-2	400	0	0	0	0	0
Group 2[6]						
REs-2[7]	200	0	0	0	0	0
RGs-2[7]	ND	200	0	0	0	0
RDs-2[7]	1,600	100	0	51,200[5]	51,200[5,8]	
Group 3[9]						
RQs-2	0	0	0	0	0	0
RRs-2[7]	200	0	0	0	102,400[5]	102,400[5]
RIs-2	0	0	0	0	0	0
RPs-2	0	0	0	0	0	0

[1]Titers are the highest dilutions of serum giving a positive reading when tested using an HIV-2 EIA kit (Genetics Systems), which is highly cross-reactive with SIV_{smm}.
[2]All infants were virus-negative at birth.
[3]Group 1: Mothers exposed to SIV between day 28–35 of gestation.
[4]Negative EIA reading at 1:100 dilution of serum, the lowest dilution tested.
[5]Virus-positive PBMC culture.
[6]Group 2: Mothers exposed to SIV between day 71–78 of gestation.
[7]Mother's milk virus-positive at 9–12 months postpartum.
[8]Died at 16 months of age.
[9]Group 3: Mothers exposed to SIV between day 146–150 of gestation.

TABLE III. PWM assays and PCR determinations in infants in maternal SIV transmission study

Animal	Age (mo.)	PWM assay	PCR	Conventional serology	PBMC virus cultures
Group 1					
RWq-2	8	+	ND	–	–
	12	ND	+	+	+[3]
RUg-2	8	+	ND	–	–
	12	+ +	+ +	–	–
RTq-2	8	–	ND	–	–
	12	+	+	–	–
RLr-2	8	–	ND	–	–
	12	ND	+	–	–
REq-2	8	ND	ND	–	–
	12	+ +	+	–	–
Group 2					
REs-2	7	+ +	ND	–	–
	11	+ +	+	–	–
RGs-2	7	–	ND	–	–
	11	–	–	–	–
RDs-2	7	+ + +	ND	–	+[1]
	11	+ + +	+	+	+[2]
Group 3					
RQs-2	5	+ +	ND	–	–
	9	ND	+ +	–	–
RRs-2	5	–	ND	–	–
	9	+	+	+[2]	+[2]
RIs-2	7	ND	ND	–	–
	11	–	–	–	–
RPs-2	6	+	ND	–	–
	10	+	–	–	–

[1]At nine months.
[2]At 12 months.
[3]At 15 months.

SRV-2, in which 83% of the offspring from SRV-2-infected macaques were found to be virus-positive at birth [26].

In the current study, all eight infants delivered by mothers infected in early and mid-gestation, and one infant delivered by an animal infected in late gestation, had low levels of maternal antibodies to SIV. This is comparable to the situation that occurs with human infants and is the key factor that makes early diagnosis of perinatal infection extremely difficult. In our study, the maternal antibodies decreased to undetectable levels by three to six months in all nine rhesus infants. Loss of maternal antibodies in rhesus infants occurred more rapidly than that seen in human infants, in which maternal antibodies have been reported to persist for more than 18 months [14,24].

The lack of a specific, sensitive diagnostic test is the major obstacle to confirming HIV infection in a timely manner in children born to HIV-infected mothers. The SIV-infected macaque model should prove useful in efforts to develop more specific and sensitive tests for the diagnosis of perinatal lentivirus infection. Although we confirmed infection by conventional serology and virus culture in only three of 12 rhesus infants born to SIV-infected mothers, preliminary PWM and PCR assays suggest that 10 of the 12 infants are infected. Continued follow-up of these infants will allow a correlation to be made between the PWM and PCR assays and subsequent seroconversion and PBMC virus-positive status. Our observation that a higher percentage of infants are PCR-positive than are seropositive or virus-positive agrees with reports for human infants born to HIV-positive mothers [11,21]. In one report, three of five seronegative children born to seropositive mothers were PCR-positive [11]. In another study, the presence of HIV-1 DNA sequences in PBMC of two seronegative, asymptomatic infants was reported and the question was raised about latent HIV infections that remain undetectable by conventional serologic tests [21]. Virus-positive, seronegative pediatric cases of HIV infection have also been reported [5,10].

Observations in our study that support the view that transmission of SIV most likely occurred by way of breast milk include 1) failure to isolate virus from multiple tissues of two stillbirths and one neonatal death, 2) failure to isolate virus from multiple cultures of PBMC of 12 rhesus infants from birth to greater than six months of age, 3) the isolation of virus from milk samples of four of 12 rhesus monkeys, and 4) the disappearance of maternal antibodies in all rhesus infants before six months of age, with subsequent seroconversion in three infants at nine and 12 months of age. Although HIV has been isolated from breast milk of asymptomatic HIV carriers [25], and postnatal infection with HIV has been documented in breast-fed infants whose mothers became infected from a postpartum blood transfusion [28,29], the role of breast-feeding in the transmission of HIV has not received a great deal of attention and transmission by this route is controversial [2]. Some reports indicate no association between breast-feeding and HIV infection [17], whereas others have indicated that breast-feeding is a significant risk in the transmission of HIV infection to children [2]. Reports such as the latter, as well as our observations in the SIV-infected macaque model, support a recommendation that infants born to HIV-infected mothers should not be breast-fed.

The SIV-infected macaque should prove to be a useful animal model to document further the role of breast-feeding in lentivirus transmission, and to evaluate potential therapeutic regimens to prevent maternal–infant transmission.

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