Seven persons subjected to right-heart catheterizations during high-altitude pulmonary edema had an average mean pulmonary-artery pressure of 58 mm Hg.[9-11] When subjects with a history of the disorder were brought to higher altitude, excessive pulmonary hypertension (mean pressure of 39±10 mm Hg) developed before the onset of symptoms or findings of edema,[12] and the pressure rose to 53±12 mm Hg during exercise. In addition, Viswanathan et al. have shown exaggerated pulmonary hypertension in response to acute hypoxia at sea level in men known to be susceptible.[13]

Total cardiac output was normal in the patient of ours in whom it was measured, and in previous reports it has been normal or high. Since the entire cardiac output passes through only one lung, the implication is that the blood flow through that lung was at least twice the normal flow, even at rest. Visscher[14] and Hultgren[2] have proposed that the distribution of pulmonary vascular resistance may become uneven during hypoxic pulmonary vasoconstriction and that the areas of lower resistance, which are overperfused, are the areas that develop edema. This concept was recently supported by evidence of uneven lung perfusion detected by means of radionuclide scanning in men susceptible to high-altitude pulmonary edema who were breathing hypoxic gas mixtures at sea level.[15] Overperfusion edema has also been described in patients with hypertensive encephalopathy.[16] Since our patients already have an overperfused lung at sea level, they would be particularly susceptible to development of areas of overperfusion edema during uneven vasoconstriction induced by high-altitude hypoxia. Furthermore, the high flow could induce endothelial damage, as proposed by Flick et al.[17] and Hyers et al.[18] The present evidence favors both high pressure and high flow as important factors in the pathogenesis of high-altitude pulmonary edema. This hypothesis is not weakened by the finding of some edema in the right lung (without a pulmonary artery) in two of our patients, since this edema could well have resulted from aspiration of edema fluid that originated in the left lung.

Physicians should be aware that the absence of a pulmonary artery can be diagnosed with an x-ray film of the chest, that high altitude can be very hazardous for persons with such an anomaly, and that any severe form of high-altitude illness at only moderate altitude should raise the suspicion that there is a predisposing factor.

We are indebted to Drs. J. Oberheide and J. Riopelle for reviewing their records, to Dr. W. B. Galloway for performing the autopsy in Patient 4, to Dr. D. McConahay for performing the heart catheterization in Patient 2, and to B. Fluitt for preparing the manuscript.

References

1. Grover RF, Hyers TM, McMurtry IF, Reeves JT. High altitude pulmonary edema. In: Fishman AP, Renkin EM, eds. Pulmonary edema. Bethesda: American Physiological Society, 1979:229-40.
2. Hultgren HN. High altitude pulmonary edema. In: Staub NC, ed. Lung water and solute exchange. New York: Marcel Dekker, 1978:437-69.
3. Elder JC, Brofman BC, Kohn PM, Charms BL. Unilateral pulmonary artery absence or hypoplasia: radiographic and cardiopulmonary studies in five patients. Circulation. 1958; 17:557-66.
4. Wyman SM. Congenital absence of a pulmonary artery: its demonstration by roentgenography. Radiology. 1954; 62:321-8.
5. Pool PE, Vogel JHK, Blount SG Jr. Congenital unilateral absence of a pulmonary artery: the importance of flow in pulmonary hypertension. Am J Cardiol. 1962; 10:706-31.
6. Shakibi JG, Rastan H, Nazarian I, Paydar M, Aryanpour I, Siassi B. Isolated unilateral absence of the pulmonary artery: review of the world literature and guidelines for surgical repair. Jpn Heart J. 1978; 19:439-51.
7. Wagenvoort CA, Wagenvoort N. Pathology of pulmonary hypertension. New York: John Wiley, 1977:294.
8. Vogel JHK, McNamara DG, Hallman G, Roseberg H, Jamieson G, McCrady JD. Effects of mild chronic hypoxia on the pulmonary circulation in calves with reactive pulmonary hypertension. Circ Res. 1967; 21:661-9.
9. Penaloza D, Sime F. Circulatory dynamics during high altitude pulmonary edema. Am J Cardiol. 1969; 23:369-78.
10. Hultgren HN, Lopez CE, Lundberg E, Miller H. Physiologic studies of pulmonary edema at high altitude. Circulation. 1964; 29:393-408.
11. Fred HL, Schmidt AM, Bates T, Hecht HH. Acute pulmonary edema of altitude: clinical and physiologic observations. Circulation. 1962; 25:929-37.
12. Hultgren HN, Grover RF, Hartley LH. Abnormal circulatory responses to high altitude in subjects with a previous history of high-altitude pulmonary edema. Circulation. 1971; 44:759-70.
13. Viswanathan R, Jain SK, Subramanian S, Subramanian TAV, Dua GL, Giri J. Pulmonary edema of high altitude. II. Clinical, aerohemodynamic, and biochemical studies in a group with history of pulmonary edema of high altitude. Am Rev Respir Dis. 1969; 100:334-41.
14. Visscher MB. Studies on embolization of lung vessels. In: Grover RF, ed. Normal and abnormal pulmonary circulation. Basel: S Karger, 1963:152.
15. Viswanathan R, Subramanian S, Radha TG. Effect of hypoxia on regional lung perfusion, by scanning. Respiration. 1979; 37:142-7.
16. Lassen NA. Control of cerebral circulation in health and disease. Circ Res. 1974; 34:749-60.
17. Flick MR, Perel A, Kageler W, Staub NC. White blood cells contribute to increased lung vascular permeability after microemboli. Fed Proc. 1979; 38:1265. abstract.
18. Hyers TM, Martinez A, Grover RF, Reeves JT. Hypoxic exercise-induced lung injury in rats. Fed Proc. 1978; 37:292. abstract.

BREAST MILK AND THE RISK OF CYTOMEGALOVIRUS INFECTION

Sergio Stagno, M.D.,
David W. Reynolds, M.D.,
Robert F. Pass, M.D.,
and Charles A. Alford, M.D.

DESPITE increasing interest, the modes of transmission of cytomegalovirus (CMV) infection, particularly in the first year of life, remain ill-defined. During the first year the rate of acquisition of CMV infection throughout the world is variable but high, as summarized in Table 1.[1-10] In populations of different ethnic and socioeconomic backgrounds, from 8 to 60 per cent of infants begin shedding virus into the urine during the first year. Intrauterine transmission, although common (it accounts for 0.4 to 2.5 per cent of cases), cannot account for the high rates of perinatal

From the departments of Pediatrics and Microbiology, the University of Alabama in Birmingham (address reprint requests to Dr. Stagno at the University of Alabama in Birmingham, Department of Pediatrics, Room 609 CDLD Building, University Station, Birmingham, AL 35294).

Supported by a grant from the National Institutes of Child Health and Human Development (5 P01-HD 10699), a General Clinical Research Grant (5 M01-RR 32), and the Robert E. Meyer Foundation.

Table 1. Rates of Urinary Excretion of CMV during the First Two Years of Life.

Country	Total No. of Infants	Percentage Excreting CMV, According to Age						
		at birth	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo	24 mo
Japan[4]	257	—	6	10	20	56	44	22	7
Thailand[8]	140	—	—	—	38	55	18	15	—
Guatemala[7] *	109	—	—	—	23	42	40	35	—
Finland[10]	105	2.3	—	12	23	35	25	33	41
Finland[2] *	148	2	—	16	32	36	—	39	—
Sweden[6]	326	1	12	—	—	—	—	23	—
U.S., Seattle[3] *	92	1	3	—	11	13	—	11	—
England[9]	118	2.5	—	—	—	9	—	—	—
England[1]	1395	0.4	—	1.8	3.2	—	5.8	—	4
U.S., Birmingham[5] *	154	1.3	2	4	7	8	8	8	9

*Prospective study.

involvement. The remarkable increase in CMV infection that occurs within the first four months after delivery suggests that infection is most likely acquired at or soon after birth. Since maternal excretion of CMV in cervical or vaginal secretions, urine, saliva, and breast milk is common in the perinatal period, the mother is believed to be the likeliest source of infection for the neonate and young infant.[3-6] So far, however, only natal transmission from infected genital secretions has been incriminated.[5] It has been suggested that transmission occurs through infected breast milk, but proof for this contention is lacking.[4,11,12] In this study, the high rate of CMV excretion into the breast milk of seroimmune women is substantiated, and evidence presented that virus can be readily transmitted to young infants through infected breast milk.

Methods

The study population comprised 396 women who had recently given birth. Colostrum (breast secretion obtained five or fewer days postpartum) or milk specimens, or both, from 278 of these women were cultured for CMV soon after delivery. Serum samples from all patients were examined for the presence of antibody and cervical-swab specimens obtained late in pregnancy (mean, 35 weeks of gestation) were examined for the presence of virus. Throat-swab specimens collected shortly after delivery and cervical-swab specimens obtained four to six weeks postpartum were examined for the presence of CMV. The 396 infants born to this group of women were assessed for cytomegaloviruria at birth.

Women who breast-fed and were willing to participate in the study were asked to bring their infants to the clinic monthly. At these visits, repeat specimens of vaginal secretions, saliva, and milk were obtained from the mothers, and urine and serum specimens from their infants.

For viral isolation, specimens were processed and examined as previously described.[5] Serum antibody titers to CMV were defined by means of anticomplement immunofluorescence and microneutralization performed according to standard methods in this laboratory.[13,14] Specific IgA antibody levels in colostrum and milk were determined by means of indirect immunofluorescence with a commercial conjugate purchased from Litton Bionetics (Kensington, Md.). For this assay twofold dilutions of the specimens in phosphate-buffered saline were tested with appropriate positive and negative controls. A titer of 4 was required as minimum evidence for the presence of CMV-specific IgA antibody in colostrum or milk.

Results

As summarized in Table 2, 38 of the 278 women (13 per cent) excreted CMV at least once into either colostrum or milk. The rates of isolation were 68 per cent among women who had just delivered congenitally infected infants, 16 per cent among those excreting CMV from other sites late in gestation, and 9 per cent among seropositive women who did not excrete CMV. As expected, none of the seronegative women shed virus.

CMV was found more often in milk (25 of 70 specimens; 36 per cent) than in colostrum (20 of 244 specimens; 8 per cent) (chi-square, $P = <0.001$). In 36 mothers who nursed infants for over one month, both colostrum and one or more specimens of milk were examined. Virus was isolated from 14 of these women between one day and nine months after delivery. Eight women shed CMV only in milk, three in both milk and colostrum, and three in colostrum only. Although CMV excretion was usually brief, five women excreted virus for periods ranging from two to six months.

Specific IgA antibodies (titer ≥ 4) were found in 11 of the 35 (31 per cent) milk specimens examined. Antibody was detected in 10 of 22 (45 per cent) of the uninfected samples and in only one of 13 (7 per cent) of the infected specimens. Thus, the lack of infectivity was significantly related to the presence of IgA antibody in the milk ($P = 0.027$, Fisher's exact two-tailed test). To investigate whether the lack of IgA antibody in the infected samples could be explained by the formation of immune complexes between CMV antigens and antibody, infectivity titers were assessed by means of a plaque assay in 10 CMV-infected milk specimens before and after incubation with anti-human immunoglobulins and C3. Immune-complex formation could not be incriminated by these approaches. Significant reduction of infectivity was detected in only one specimen after incubation with anti-C3 but not with anti-immunoglobulins.

To define whether CMV could be transmitted by breast milk, the infants of 28 women shedding CMV only in breast milk were studied prospectively; 19 of them were breast-fed, and nine were exclusively bottle fed. None of the infants had been infected in utero or received blood transfusions. Whereas none of the nine bottle-fed infants became infected, 11 of the 19 infants (58 per cent) fed infected breast milk acquired CMV

Table 2. Rate of CMV Isolation from Colostrum or Breast Milk, or Both.

Maternal Status	No. Excreting CMV/ No. in Group *
Mothers of congenitally infected infants	11/16 (68)
Women excreting CMV from other sites †	8/49 (16)
Seropositive women not excreting CMV †	19/200 (9)
Seronegative women †	0/13 (0)
Total	38/278 (13)

*Figures in parentheses denote percentages.
†Late in gestation.

Table 3. Association between Maternal Excretion of CMV from Various Sites and Subsequent Infection of the Infant.

Only Site of Maternal Excretion	No. of Infants Infected/ No. Exposed *
Breast milk	
Breast-fed infant	11/19 (58)
Bottle-fed infant	0/9 (0)
Cervix	
3d trimester & postpartum	8/14 (57)
3d trimester	18/68 (26)
1st & 2d trimester	1/8 (12)
Urine †	0/11
Saliva ‡	0/15
Nonexcreting women	
Bottle-fed infant	0/125
Breast-fed infant	1/11 (9)

*Figures in parentheses denote percentages. †Late 3d trimester.
‡Excretion 1 day postpartum.

infections (Table 3). These infants became viruric between four weeks and four months of age except for one who became viruric at nine months of age, three months after his mother had her first CMV-positive milk specimen. In all infected infants, infection was established in the presence of considerable levels of maternally derived neutralizing antibody (geometric mean titers = 48; range, 8 to 256).[15] Between the mothers who did and did not transmit CMV to their infants, respectively, there were no important differences in age (mean of 25 years and range, 20 to 34 years versus mean, 22 years and range, 16 to 25 years), the number of siblings in their household (two siblings in 11 households versus two in eight), race, the duration of lactation (9.5 weeks versus 9.0 weeks), duration of CMV excretion in milk, presence of IgA-specific antibody (0 of 4 versus 0 of 4) and the infectivity titers of CMV in milk (1 to 2.3 versus 1 to 2.3 log 10 $TCID_{50}$ per 0.2 milliliter).

The association between maternal excretion of CMV from various sites and the subsequent acquisition of infection by the infant (from birth to six months of age) is summarized in Table 3.[5] When fed infected breast milk or exposed to CMV in the genital tract during delivery, the rate of infection in young infants was high and nearly the same — 58 per cent in those fed infected breast milk and 57 per cent in those exposed to CMV during delivery. With viral shedding into the maternal genital tract late in gestation but not postnatally or earlier in pregnancy, the frequency of infection in the offspring was less, 26 per cent in those whose mothers had viral shedding into the genital tract during the third trimester fed infected breast milk and 12 per cent in those whose mothers had shedding during the first and second trimesters only. In contrast, perinatal infection was not associated with isolated maternal excretion of CMV into urine or saliva. Only one of the 136 infants born to women who did not excrete CMV became viruric, at four months of age; this baby was among the 11 who were breast-fed. Unfortunately, in this particular case only two specimens of milk were studied at two and 91 days postpartum; both were reported negative for CMV.

Of the 39 infected infants, only one (delivered through an infected birth canal) acquired a severe pneumonitis, at five weeks of age. After extensive microbiologic and immunologic studies failed to demonstrate any other pathogens it was concluded that the pneumonitis was most likely of CMV origin. The microimmunofluorescence test for antibodies to *Chlamydia trachomatis* remained negative after four months of follow-up (kindly performed by Drs. Alexander and Wang, Seattle, Wash.). At a mean age of 51 months (range, nine to 93 months), growth and development and the results of psychometric evaluations and assessments of hearing and vision were entirely within normal limits in all 39 infected infants. Despite minimal morbidity, chronic excretion of CMV in both urine and saliva persisted in all patients for over two years (range, 27 to 55 months).

Discussion

The rate of isolation of CMV from breast milk in this predominantly black population of women of low socioeconomic status was 13 per cent, a figure that exceeds our previously reported rates of viral excretion from other sites (throat, 2.4 per cent; urine, 4.7 per cent; and cervix, 10.1 per cent) when examined in the perinatal period.[16] Although the proportion of women shedding CMV into breast milk may appear high, it must be viewed as a minimum, since sampling was only sporadic and, therefore, not likely to detect intermittent or short-term excretion. Furthermore, in the majority of the women, virologic assessments were done only in colostrum, which, in this study as in a previous report by Hayes et al.,[11] was positive for virus less often than milk was. More important than the finding that CMV appears commonly in the breast milk of seropositive mothers is the demonstration that 58 per cent of infants fed CMV-infected breast milk acquired the infection. Viruria appeared in these infants between 30 and 120 days after exposure, an incubation period similar to that observed in infants exposed to CMV in the genital tract during delivery[5] and to that of adults with postperfusion CMV mononucleosis.[17]

The findings reported here and those from previous studies of transmission of CMV indicate that the occurrence of CMV infection during the first six months of life should, in the absence of blood transfusion, be viewed as the result of mother-to-infant transmission.[2-5] The presence of siblings in the home has not been related to increased risk of early CMV infection.[3,5] This report and previous studies have identified three major routes of transmission: transplacental, exposure to vaginal secretions (natal), and breast milk. Other possible maternal sources such as saliva or hand transfer do not appear to be important since perinatal CMV infections have not been associated with isolated shedding of virus into the maternal pharynx or urinary tract. The relative importance of the three major routes in any given population will be influenced by the prevalence of breast-feeding, the rate of seropositivity, maternal age, and probably other

factors such as race and socioeconomic background that operate by mechanisms that are not yet known. The contribution of congenital infection to the overall rate of infection during the first year of life is rather modest (0.4 to 2.5 per cent) in all populations, as shown in Table 1. The relative importance of the natal route (exposure to CMV during delivery) is difficult to ascertain, since only three of these studies provide rates of CMV isolation from genital-tract secretions. The prevalence of excretion in the third trimester of pregnancy was 28 per cent in Japan and 11 per cent in Birmingham, Ala.[4,5] The collaborative study of Manchester reported a 3.5 per cent rate among nonpregnant women.[1] Thus, from the risk of transmission illustrated in Table 3 (12 to 57 per cent) we can expect that anywhere from 3 to 15 per cent of the Japanese, 2 to 6 per cent of the American, and 0.3 to 2 per cent of the British cohorts could have become infected during birth. In the Birmingham study, natal transmission accounted for all but one of the infections documented within the first six months of life.[5] In contrast, in Japan more than two thirds of the infections in infants still cannot be explained by this route of transmission.[4] What is remarkable is that in Japan, as in Guatemala, Finland, and Thailand, where the rates of CMV infection within the first year of life are extremely high (39 to 56 per cent), the practice of breast-feeding is almost universal, and the majority of women of childbearing age are seroimmune for CMV.[3,4,7,8] If in these countries immune women who had recently given birth excreted CMV into milk as often as they did in the present study, and if we assume that the risk of transmission to their infants was similar to the risk encountered in our study, then breast milk was the most likely source of the high rate of CMV infections that occurred within the first year of life.

In this study, infections acquired during birth or from breast milk were not prevented by substantial levels of maternally derived neutralizing antibody that were present at the time of exposure as well as during the period in which blood-borne spread is most likely to have occurred.[15] Although passive humoral immunity was incapable of preventing these naturally acquired infections, it may explain, at least in part, why morbidity was only minimal.

In summary, in populations with a high rate of CMV seropositivity among women of childbearing age, transmission through breast milk seems to be the reason for the rapid and common acquisition of CMV that occurs among breast-fed infants. Because the infection produces minimal morbidity and leads to chronic shedding of virus into urine and saliva, which may facilitate horizontal CMV spread in later months, it must be viewed as a form of natural immunization. Thus, the minimal risk associated with transmission of CMV through breast milk is clearly outweighed by the well-established value of breast-feeding. We must be cautious, however, with expressed banked milk and wet-nurses, since CMV-infected milk might inadvertently be given to infants born to seronegative women or to premature infants, who generally do not receive sufficient quantities of specific transplacental antibodies. It is hoped that means to render the milk noninfectious without destroying its valuable properties will become available in the near future.

References

1. Cytomegalovirus infection in the north west of England: a report on a two-year study: collaborative study. Arch Dis Child. 1970; 45:513-22.
2. Granström M-L, Leinikki P, Santavuori P, Pettay O. Perinatal cytomegalovirus infection in man. Arch Dis Child. 1977; 52:354-9.
3. Levinsohn EM, Foy HM, Kenny GE, Wentworth BB, Grayston JT. Isolation of cytomegalovirus from a cohort of 100 infants throughout the first year of life. Proc Soc Exp Biol Med. 1969; 132:957-62.
4. Numazaki Y, Yano N, Morizuka T, Takai S, Ishida N. Primary infection with human cytomegalovirus: virus isolation from healthy infants and pregnant women. Am J Epidemiol. 1970; 91:410-7.
5. Reynolds DW, Stagno S, Hosty TS, Tiller M, Alford CA Jr. Maternal cytomegalovirus excretion and perinatal infection. N Engl J Med. 1973; 289:1-5.
6. Ahlfors K, Ivarsson S-A, Johnsson T, Svensson I. Congenital and acquired cytomegalovirus infections: virological and clinical studies on a Swedish infant population. Acta Paediatr Scand. 1978; 67:321-8.
7. Cruz JR, Mata LJ, Urrutia JJ. Citomegalovirua durante el primer año de vida: estudio prospectivo en una poblacioń indigena de Guatemala. Bol Of Sanit Panam. 1977; 83:218-22.
8. Olson LC, Ketusinha R, Mansuwan P, Snitbhan R. Respiratory tract excretion of cytomegalovirus in Thai children. J Pediatr. 1970; 77:499-504.
9. Stern H. Isolation of cytomegalovirus and clinical manifestations of infection at different ages. Br Med J. 1968; 1:665-9.
10. Leinikki P, Heinonen K, Pettay O. Incidence of cytomegalovirus infections in early childhood. Scand J Infect Dis. 1972; 4:1-5.
11. Hayes K, Danks DM, Gibas H. Cytomegalovirus in human milk. N Engl J Med. 1972; 287:177-8.
12. Diosi P, Babusceac L, Nevinglovschi O, Kun-Stoicu G. Cytomegalovirus infection associated with pregnancy. Lancet. 1967; 2:1063-6.
13. Stagno S, Reynolds DW, Smith RJ. Use of isolated nuclei in the indirect fluorescent-antibody test for human cytomegalovirus infection: comparison with microneutralization, anticomplement, and conventional indirect fluorescent-antibody assays. J Clin Microbiol. 1978; 7:486-9.
14. Stagno S, Reynolds D, Tsiantos A, et al. Cervical cytomegalovirus excretion in pregnant and nonpregnant women: suppression in early gestation. J Infect Dis. 1975; 131:522-7.
15. Reynolds DW, Stagno S, Reynolds R, Alford CA Jr. Perinatal cytomegalovirus infection: the influence of placentally transferred maternal antibody. J Infect Dis. 1978; 137:564-7.
16. Knox GE, Pass RF, Reynolds DW, Stagno S, Alford CA. Comparative prevalence of subclinical cytomegalovirus and herpes simplex virus infections in the genital and urinary tracts of low income, urban females. J Infect Dis. 1979; 140:419-22.
17. Lang DJ, Hanshaw JB. Cytomegalovirus infection and the postperfusion syndrome: recognition of primary infection in four patients. N Engl J Med. 1969; 280:1145-9.