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Cytomegalovirus infection: epidemiology and association with congenital malformations

by

De Schryver A. [1], De Backer G. [1], Van Renterghem L. [2]

Abstract

Cytomegalovirus (CMV) is the most common viral cause of intrauterine infection, and is the major infectious factor known to be associated with congenital mental retardation and deafness. The number of children with serious handicaps attributable to CMV is comparable to that of children born with congenital rubella in a non-epidemic year in the era before vaccination. Studies have shown the importance of breast feeding and child-rearing practices. The occupational risk for health care workers and child care providers is variable, but clearly exists particularly when caring for small children is considered.

Prevention policy is geared towards health care workers and screening of blood and blood products. In health care workers and child carers prevention must be based on careful handwashing and avoidance of contact with excretions and secretions of children. Screening of pregnant women is currently not recommended for public health purposes.

[1] Departement of Public Health, University of Gent, UZ Blok A, De Pintelaan 185, 9000 Gent.
[2] Departement of clinical chemistry, microbiology and immunology, University of Gent, De Pintelaan 185, 9000 Gent.

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Introduction

The original description of the relation between cytomegalovirus infection (CMV) and diseases of the newborn dates back to the beginning of the 20th century when large inclusion-bearing cells were noted in organs of infants who had died due to a variety of clinical syndromes (1).

In the fifties the virus causing these lesions was isolated (2, 3).

Cytomegalovirus infection is now the most common viral cause of intrauterine infection and is the major infectious factor known to be associated with congenital mental retardation and deafness (4-7). The number of children with serious handicaps attributable to CMV is comparable to that of children born with congenital rubella in a non-epidemic year in the era before vaccination (8). The infection is thought to affect approximately 1 to 2% of all newborns in the United States and Western Europe (9, 10). Although only 10% or less of congenitally infected infants have symptoms as a result of CMV infection, CMV remains the most common, recognized cause of virus-induced mental retardation.

Moreover there are some indications that this cause of fetal damage is becoming more important, due to a number of socio-economic changes (11).

Virology

CMV is a highly host-specific herpesvirus that produces characteristic large cells with intranuclear inclusions. Human CMV is one of the human herpesviruses.

CMV shares with other herpesviruses, such as Herpes Simplex, Varicella-Zooster and Epstein-Barr viruses, the unique ability to remain latent in tissues after it has occasioned an acute infection in the host. On the basis of epidemiologic data gathered primarily from transplant recipients, we can now say that the dictum «once infected, always infected» probably applies to CMV. Unlike herpesviruses such as Herpes Simplex

and Varicella-Zooster viruses, which remain latent in highly restricted areas of the body, latent CMV can be found in multiple body sites (12).

Viral excretion of the original infecting strain may resume at any time; therefore, CMV apparently becomes latent. Not only can a latent infection occur, but reinfection with a second strain of CMV may occur in both immunocompetent and immunocompromized individuals (13).

Clinical manifestations of congenital disease

Congenital CMV infection can give rise to very different syndromes and become only apparent during the first years of live (9). In serious cases, which account for approximately 10% of cases the following symptoms are seen:pre- and dysmaturity, hepatosplenomegaly including jaundice, anemia and trombocytopenia, microcephaly and other neurological symptoms leading to deafness, epilepsy, spastic paresia and mental retardation. The frequency of these lesions is given in table 1 (14).

In most affected children mortality can reach 20% in the first year of life and death can occur during the neonatal period or in the first months of life (15). More important still is the fact that almost 90% of children who survive a congenital CMV infection have an abnormal intellectual development or impaired hearing.

TABLE 1

Frequency of clinical findings in children with symptomatic congenital CMV infection in the newborn period (14)

Abnormality	Percentage
Petechiae	76
Jaundice	67
Hepatosplenomegaly	60
Microcephaly	53
Small for gestational age	50
Prematurity	34
Lethargy-hypotonia	27
Poor suck	19
Purpura	13
Seizures	7

Risk of fetal damage after infection during pregnancy

Transmission of CMV to the developing fetus during pregnancy is highly dependent on immunity to the virus of the mother before conception (16). Studies have documented transmission rates of 35-50% after CMV infection during the pregnancies of women lacking preconception seroimmunity to CMV (9,16,17). In contrast the rates of fetal transmission in women with such immunity are 0.2 to 2.0%, depending on the patient population (16). Transmission when there is preexisting immunity is thought to occur secondary to recurrence of maternal infection and less frequently to reinfection during pregnancy (9,16).

Preconception seroimmunity to CMV is also associated with protection from symptoms at birth and with fever and less severe long-term central nervous system sequelae associated with congenital CMV infections (18,19). The rate of symptomatic congenital infection at birth in offspring of women with preconception seroimmunity is near zero versus 10-15% in infants born to women who had primary maternal CMV infection during pregnancy (9,16,20). Recent studies have also documented more favourable long-term outcome in congenitally infected infants born to CMV infected women than in those born to mothers with primary infections (20).

In 10% of children infected in utero due to a primary infection by CMV in the mother a serious syndrome with mortality up to 20% is noted. More than 90% of the survivors show sequelae (7,21). In 90% infants asymptomatic at birth, 5-15% get sensory hearing loss, bilateral in 50%, microcephaly, mental retardation and impairment in speech development; globally 15 to 20% of congenitally infected children show serious sequelae. The presence of sequelae in asymptomatic children is thought to be related to the moment of infection: early infection seems to give rise to more sequelae (22, 23).

Recurrent infection

Recurrent (or a renewed) maternal infection during pregnancy is considered less dangerous to the fetus than is primary infection, although most women who excrete virus during pregnancy do so as a result of recurrent infection. This intra-uterine infection most often follows maternal viral reactivation, which causes a lower rate of fetal complications (9, 24, 25).

However, some other studies have not confirmed this finding (9, 20).

The reasons for these inconsistencies are probably due to other differences between the groups and exposure to other noxes such as alcohol and drugs.

Epidemiology of CMV infections

Studies have tried to determine the frequency and prevalence of antibody to CMV in human populations in different parts of the world. In table 2, the results of a WHO cooperative study involving equal numbers of male and female healthy blood donors between 20-40 years of age are shown. The prevalence of antibody in that study ranges from 40 to 100% (26). Although these studies are mostly not perfectly matched for age and other determinants of CMV infection, it can be concluded that there exists a rough correlation between the prevalence of antibody and the socioeconomic conditions of the population. The prevalence of antibody is low in Europe, Australia and parts of North America, whereas it is significantly higher in the developing countries of Africa and Southeast Asia.

TABLE 2
Prevalence of antibody to CMV in adult populations in various parts of the world (26)

Location	Percentage with CF antibody to CMV
Lyon, France	40
Freiburg, Germany	42
St Gallen, Switzerland	45
Albany, New York, USA	45
Melbourne, Australia	54
Stockholm, Sweden	60
Manchester, England	61
Honolulu, Hawai, USA	67
Houston, Texas, USA	79
Buenos Aires, Argentinia	81
Bratislava, Slovakia	83
Port of Spain, Trinidad	86
Groenland	88
Mauritius	89
Hong Kong	94
Anchorage, Alaska, USA	94
Sendai, Japan	96
Dar es Salaam, Tanzania	98
Morocco	98
Fiji Islands	100
Manilla, Philippines	100
Entebbe, Uganda	100

The prevalence of CMV infection increases with age, but, according to geographic, ethnic, and socioeconomic backgrounds, the patterns of acquisition of this infection vary widely among populations. CMV is acquired earlier in life in developing countries and among the lower socioeconomic strata in industrialized countries. Differences between populations can be particularly striking during childhood. Presumably, these significant differences are the reflection of factors that account for increased exposure to CMV such as crowding, breast-feeding, sexual practices, and certain rearing practices.

Transmission of CMV

CMV transmission occurs by direct or indirect person-to-person contact. Known sources of the virus include urine, oropharyngeal secretions, cervical and vaginal secretions, semen, milk, tears and blood (27). Under special circumstances fomites may also play a rol, since CMV has been shown to retain infectivity for hours on plastic surface and has been isolated from randomly selected toys and surfaces in day-care centers (28, 29).

The five major ways of transmission are:

- via oropharyngeal secretions and urine:infected persons (mostly children) tend to carry the virus in the respiratory tract and urine for long periods and can transmit the virus to other persons; (30,31)
- sexual contact:both homosexual and heterosexual transmission occur and play an important role in the dissemination of the virus (32)
- via blood transfusion, bone marrow and solid-organ transplantation (33-36)
- transplacental during pregnancy. The frequency of congenital CMV infection at birth ranges from 0.5 to 1.5% and occurs in about 1% of all deliveries (12). However, the percentage of neonates who are symptomatic is small.
- via breast-feeding.

Particularly the combination of breast-feeding and child-rearing practices, notably the use of day-care centers is important to understand the epidemiology of CMV.

Role of breast-feeding and day-care centers

Studies carried out in the past 15 years indicate that breast-feeding and child-rearing practices singly or in combination are two of the most powerful indicators influencing the rate of acquisition of CMV in the various populations (37,38). Breast-feeding is the major factor during the first year of life with CMV excretion rates of > 50% observed in countries where the majority of women are seropositive and breastfeed their infants. The rapid increase in the rate of infection that generally takes place after the first year of life is the result of close contact and exposure to children who acquired CMV infection from a maternal source (i.e. in utero, from exposure to genital secretions at birth, or from breast milk) (27).

Already in 1971, it was suggested that the high rate of seropositivity among Swedish children was probably due to the frequent use of day-care centers (39).These high rates of CMV infection among children attending day-care centers were later confirmed in Sweden and have been reported in several studies in the United States (31, 37, 40-47). However, studies in the United Kingdom and France have only partially confirmed these results (48-50). Differences in the organization of day-care, including the number of children catered for, their age mix and social background, as well as different patterns of acquisition of cytomegalovirus infection in different communities, may explain the difference in these findings.

Although it is clear that children between one and three years of age who have daily close contact are likely to acquire CMV from each other, we can only speculate on the routes of transmission. Infection rates have remained low for infants below 12 months of age who occupy the same small room, a result indicating that airborne or respiratory-droplet transmission probably does not play a significant role in the spread of infection (15, 37). Since the incidence of infection is highest in children between one and three years of age,when the children have direct contact, high rates of salivatary shedding of CMV, and frequent exchange of oral secretions, it is likely that transfer of virus occurs through saliva on hands or toys. The recovery from toys and the demonstration that infectious virus persists on surfaces for hours (28, 37, 43) also support a role for environmental contamination.

It can be concluded that transmission among children does occur in day care centers, but that it is not always and everywhere as important as transmission route.

Prevalence studies in selected groups of the population
CMV in young children

As already pointed out in some studies, about 20% of children become infected during the first year of life (51). Wide variations in proportions of children excreting the virus in urine or saliva have been reported. In a Swedish study of hospitalized children there were 6.4% excretors in children under 6 months and 23.4% in children between 6 and 11 months. Most of these children excrete the virus up to 3 years (52).In studies of day care centers, up to 25% of children < 3 years old excrete CMV (53).

In general, CMV is acquired earlier in life in developing countries than in industrialized countries. In industrialized countries, CMV is acquired earlier in life among populations of low socioeconomic status (49, 54).

Reasons for differences in age at acquisition of CMV among populations differing in socioeconomic level or living circumstances have not been established, but specific child-rearing practices appear to influence of CMV in children.

The importance of breast-feeding and transmission in milk has already been cited. Also the role of day care centers has been stressed.

CMV infection in adults

Differences in age-related prevalence of antibody among groups extend into adulthood, with seropositivity rates among women of child-bearing age ranging from 30 to 100% depending on the origin and socioeconomic level. In the absence of incidence studies, which are certainly very difficult to perform for CMV, prevalence in different age groups can give an estimation on the incidence in this group. In a recent study the prevalence of seropositivity in Gent was determined in a random sample of the general female population aged 25-39 years and is given in table 3 (55). The prevalence varied from 26.3% in the youngest age group to 44.1% in the oldest one. Using these data, and assuming a linear increase in the course of time, the yearly incidence of CMV infection in women of child-bearing age can be estimated at 2% per year.

Pregnant women

As the prevalence of seropositivity to CMV is critical with regard to the possible impact of congenital infections caused by CMV, also preg-

TABLE 3
Prevalence of CMV seropositivity in the female population aged 25-39 years in Gent, Belgium (55)

Age group	N	Prevalence in %	95% confidence interval
25-29	76	26.3	16.3 - 36.3
30-34	69	36.2	24.8 - 47.6
35-39	84	44.1	33.5 - 54.7
Total	*229*	*35.8*	*29.6 - 42.0*

nant women have been studied. In table 4 the prevalence in pregnant women in a number of studies is given. Prevalence is determined by a number of demographic factors such as ethnic group, education, being breast-fed as an infant, child rearing practices and maternal age (67) which are not always detailed in these studies. Data from Belgium show that the prevalence of CMV seropositivity in pregnant women is on the low side compared to studies in high social class groups in other countries (i.e. the United States)(65,66).

Risk of congenital infection in Belgium

The prevalence of congenital CMV infection in different studies is given in table 5 and ranges between 1.2 and 15.8 per thousand births. Increased rates of congenital infection have been associated with maternal age, lower social class, single marital status and lower parity (8).

Using the incidence of 2% per year in women of childbearing age, assuming a transmission to the fetus after primary maternal infection of 40% (68), 10% of congenitally infected being symptomatic at birth and 15% having developmental, mostly neurological abnormalities (20), we have estimated the total number of children with symptoms of congenital CMV infection in Flanders based on the number of births for the year 1996 (69)(see table 6). Although this number seems rather modest, it is higher than the number of cases of congenital spina bifida or chromosomal abnormalities of that year.

Occupational risk

Many epidemiological studies have investigated cytomegalovirus seroprevalence and seroconversion rates among health professionals.

TABLE 4
Prevalence of antibody against CMV in pregnant women

Place (reference)	Number	Social class	Mean age	Prevalence (in%)
Abidjan, Ivory Coast (56)	1 038	–	NG *	99.9
Sendai, Japan (57)	574	–	NG	92.2
Jefferson County, Kentucky;USA (58)	100	Low	21.6	88.0
Birmingham, Alabama; USA (16)	1 014	Low	22.6	82.4
Alabama; USA (9)	4 078	Low	21.3	76.6
Beer-Sheva, Israël (59)	567	–	NG	73.0
Malmö, Sweden (60)	4 382	–	NG	72.0
London, England (61)	1 040	–	NG	66.6
Leeds, England (62)	1 886	–	NG	62.6
London, England (63)	14 789	–	NG	56.0
Birmingham, Alabama; USA (16)	2 698	High	26.5	55.4
Edinburgh, Scotland (64)	4 446	–	NG	54.5
Birmingham, Alabama; USA (9)	12 140	High	26.6	53.5
Brussels, Belgium (65)	1 771	–	NG	51.4
Jefferson County, Kentucky, USA (58)	100	High	28.5	48.0
Jefferson County; Kentucky, USA (58)	100	High	26.9	50.0
Leuven, Belgium (66)	1043	–	NG	28.3

* NG = not given

These studies suggest that rates of acquisition of the virus are similar to those found in the general population, and that hospital staff are not at increased risk of acquiring cytomegalovirus infection, even if they are working in pediatric, neonatal intensive care, or acute renal units (70,71). It is likely that this reflects the protective nature of normal infection control procedures within the health care setting.

As prevalence of CMV excretion in children in day care settings in the US has been found to be high, it comes to no surprise that studies have identified high rates of seroconversion among daycare workers (72-74).

TABLE 5
Prevalence of congenital CMV infection (virusisolation).

Place(reference)	Number of neonati	Social class	Prevalence (per 1000)
Malmö, Sweden (52)	326	–	1.2
Sendai, Japan (57)	10 218	–	1.3
Abidjan, Ivory Coast (56)	2 155	–	1.4
London, England (8)	13 107	–	2.4
London, England (6)	14 200	–	3.0
Hamilton, Ontario; Canada (21)	15 212	–	4.2
St Gallen, Switzerland (56)	–	–	5.0
Birmingham, Alabama; USA (9)	8 545	High	5.5
Birmingham, Alabama; USA (16)	2 699	High	5.9
London, England (61)	702	–	7.1
Edinburg, Scotland (64)	1 405	–	11.4
Birmingham, Alabama; USA (9)	2 579	Low	14.0
USA (16)	1 014	Low	15.8

TABLE 6
Estimation of public health consequences of congenital CMV infection in Flanders, based on 1996 data

Variable	Estimated value
N of live births	63 550
N of seronegative pregnant women (64.2%)	40 799
N of pregnant women infected (2%)	816
Transmission of CMV to fetus (40%)	326
Newborns	
N of newborns with symptomatic disease (10%)	33
N of asymptomatic infections at birth	293
N with sequelae (15%)	44
Total number with sequelae	77

Differences in the organization of daycare, including the number of children catered for, their age mix and social background, as well as different patterns of acquisition of cytomegalovirus infection in different communities, may explain why similar findings have not been confirmed elsewhere (48).

Nevertheless, it is reasonable to assume that nursery staff do not routinely practise the kind of infection control procedures carried out in hospital, but deal with children more as one would at home. Many of these workers come into daily contact with large numbers of young children, some of whom will be excreting cytomegalovirus in saliva or urine.

Prevention policy

As the health damage caused by CMV is not the infection as such but the possible congenital infection, prevention must particularly be focused on pregnant women, and, more generally, on women of child-bearing age. Approaches for prevention include measures in people occupationally caring for young children, screening of blood and blood products and screening of pregnant women. As young children are the largest source of infection, much attention will be given to prevention in people working with those children.

People caring for young children

If strictly adhered to, blood and body fluid precautions will protect both patients and personnel (75). Although CDC guidelines for universal precautions do not apply to nasal secretions, sputum, or urine unless they are contaminated with blood, pregnant health care workers should assume that all body fluids are possibly infectious. They should practice frequent hand washing after patient contact. When they perceive that they are most likely to be exposed to body fluids or when they are handling urine and respiratory secretions, they should wear gowns and gloves.

The growing awareness that nursery staff may be exposed to many infections, including hepatitis B and HIV, has highlighted the need to ensure that high standards of hygiene are maintained within the day nursery. In this context, the overall standard of hygiene practised within a day nursery should be more than adequate to prevent the acquisition of cytomegalovirus. Health education about infections in the community,

including cytomegalovirus, should include information about their modes of transmission and means of control, and be a fundamental element in the training of nursery staff and other professionals working with young children in the community. As far as cytomegalovirus is concerned, particular attention should be paid to avoiding the exchange of saliva, and hands should be washed after changing nappies or helping children to use the toilet.

Screening of blood & blood products

According to the Law of 4.07.1994 taking of blood for blood transfusion is not allowed from people with an infectious disease. Although it is not stated in the law which infectious diasease is referred to, the practice in Belgium is to screen blood for CMV serology and give CMV-negative blood to patients with special risk for transfusion-transmitted CMV infection (76).

Screening of pregnant women

Currently, little information exists regarding the role of routine screening of pregnant women in an attempt to prevent congenital CMV infection and serologic testing of all pregnant women to identify those who have acquired primary infection is not recommended for routine use (13, 67, 77).

The following arguments are against screening.

1. Reliability of serologic tests performed in clinical laboratories is questionable (sensitivity of only 75%)(20).

2. Screening of pregnant women requires repetitive serum samples of all seronegative patients and thus in practice it is difficult to obtain these.

3. Even if seroconversion is diagnosed during pregnancy, in utero techniques are of limited value (25,65). These tests are not sufficiently sensitive, and even a positive result may identify infants who are not necessarily affected.

However, screening before conception can be advised if it is limited to women at high risk for acquiring infection so that they could be given

counseling accordingly. In Belgium this policy has a legal basis since the Royal Decree of 4.08.96 on protection of employees against biological agents which stipulates that employees must undergo a medical examination before being exposed to biological agents like CMV. This examination should include a serological test if appropriate. On the basis of the results of these tests, seronegative employees working in high-risk setting could be removed from work when pregnant. This possibility, which leaves the woman at risk for some time during the beginning of pregnancy, is actually already accepted by the Belgian Fund for Occupational Diseases.

Conclusion

After the introduction in industrialized countries of routine immunization against rubella of all young women the incidence of congenital rubella syndrome decreased dramatically. Consequently, congenital CMV infection has become the most common infectious cause of serious fetal damage. Up till now data in Belgium on the risk for congenital CMV infection and groups at risk have been scarce. Therefore studies are needed to estimate this risk an — preferrable at the same time — study the possibilities and effectiveness of preventive measures.

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