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REVIEW

Pediatric roots of cytomegalovirus recurrence and memory inflation in the elderly

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Abstract

The establishment of a lifelong latent infection after resolution of primary infection is a hallmark of cytomegalovirus (CMV) biology. Primary infection with human CMV is possible any time in life, but most frequently, virus transmission occurs already perinatally or in early childhood. Many years or even decades later, severe clinical problems can result from recurrence of infectious virus by reactivation from latency in individuals who undergo immunocompromising medical treatment, for instance, transplant recipients, but also in septic patients without canonical immunosuppression, and in elderly people with a weakened immune system. The diversity of disease manifestations, such as retinitis, pneumonia, hepatitis, gastrointestinal disease, and others, has remained an enigma. In clinical routine, seropositivity for IgG antibodies against human CMV is taken to indicate latent infection and thus to define a qualitative risk of recurrence, but it is insufficient as a predictor for the quantitative risk of recurrence. Early experimental studies in the mouse model, comparing primary infection of neonatal and adult mice, led to the hypothesis that high load of latent viral genomes is a better predictor for the quantitative risk. A prolonged period of virus multiplication in the immunologically immature neonatally infected host increased the risk of virus recurrence by an enhanced copy number of latent virus genomes from which reactivation can initiate. In extension of this hypothesis, one would predict today that a higher incidence of reactivation events will also fuel the expansion of virus-specific T cells observed in the elderly, a phenomenon known as "memory inflation". Notably, the mouse model also indicated a stochastic nature of reactivation, thus offering an explanation for the diversity and organ selectivity of disease manifestations observed in patients. As the infection history is mostly undefined in humans, such predictions from the mouse model are difficult to verify by clinical investigation, and moreover, such questions were actually rarely addressed. Here, we have surveyed the existing literature for reports that may help to retrospectively relate the individual infection history to the risk of virus recurrence and recrudescent organ disease.

Keywords Latent infection · Mouse model · Latent viral genome · Transmission · Neonatal infection · Immune response · CD4 T cells · Recurrence incidence · Reactivation

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Introduction: clinical background

Human cytomegalovirus (HCMV) has not evolved mechanisms that harm humans. This clinical fact contradicts the misnomer "immune evasion" for mechanisms by which CMVs, including HCMV, dampen the immune control to achieve a virus–host balance. The prevalence of HCMV infection varies substantially. In multivariate analysis in the US, high prevalence was found to be associated with older age, certain ethnicities, female sex, higher household and/or daycare center crowding, and parameters summarized as "socioeconomic status" (for a review, see [1]). Individuals infected with HCMV usually experience no apparent disease or harmful adverse effects, unless the immune system

is compromised. In principle, primary infection can occur at any time in life upon host-to-host transmission by mucosal exposure to saliva of a virus-shedding person. Most frequently, transmission occurs in early childhood, either perinatally by breast feeding or by intrafamiliar transmission. Large group daycare facilitates child-to-child transmission. Recent changes in life style have caused a decline in the frequency and duration of breast feeding, which reduced the incidence of this route of transmission and thus the population prevalence of HCMV infection. This has led to an increasingly large proportion of women who did not become immune and thus are susceptible to HCMV. Severe neonatal disease occurs if a woman acquires a primary HCMV infection during pregnancy (for reviews, see [1, 2]).

Productive primary infection in otherwise healthy persons is rarely diagnosed and passes unnoticed due to only mild and unspecific "feverish" symptoms. After resolution of productive infection by mechanisms of innate and adaptive immunity, the viral genome is maintained in a replicatively silenced state that is characterized by a mostly closed viral chromatin-like structure and absence of productive cycle transcripts, which explains the absence of infectious virus. This stage is referred to as "latency" (for details and references, see review articles in this issue of *MMIM* [3, 4]). Recurrence of HCMV from latency frequently causes disease in immunocompromised patients. These patients are immunocompromised due to iatrogenic interventions to prevent disease and death from other etiologies. Risk groups include patients receiving immunosuppressive drugs after solid organ transplantation (SOT) and hematopoietic (stem) cell transplantation (HSCT; HCT) and those immunocompromised by HIV (for reviews, see [5, 6]). To date, there is no explanation for the diversity in the clinical manifestations occurring in these HCMV infected immunocompromised patients.

Regardless of age at the time of primary infection, otherwise healthy people "seroconvert" by a B-cell response producing CMV-specific antibodies in parallel to the establishment of viral latency. In clinical routine of transplantation medicine, seropositivity for IgG antibodies against HCMV is used to indicate past CMV encounter(s) that led to latent infection of either transplant donor (D) or recipient (R) or both. This defines a qualitative risk of recurrence of donor's and/or recipient's virus in constellations D^+R^-, D^-R^+, and D^+R^+, respectively, but does not predict the risk of recurrence in quantitative terms (for reviews, see [4, 7]). Here, we pursue the hypothesis that age/immune system maturity at the time of infection matters in regard to risk of virus recurrence and disease later in life. Specifically, a picture emerges suggesting that a prolonged primary infection with high viral intra-host spread leads to a high burden of latent viral genomes in multiple host organs and that the incidence of recurrence positively correlates with the copy number of latent viral genomes from which reactivation can initiate. We propose that there exists a causal link between infection history, latent viral genome burden in organs, and the phenomenon of "memory inflation" in the elderly.

Early messages from a mouse model

Not all medical questions on CMV can be feasibly addressed by clinical investigation. One such question is the influence of the individual infection history on the load of latent viral DNA in tissues and the risk of virus recurrence. One reason is that time, dose, and route of the past primary HCMV infection of latently infected CMV-IgG^+, but otherwise healthy volunteers enrolled in clinical studies are unknown variables. Another reason is that in a prospective cohort study, a longitudinal sampling of biopsies from multiple organs is beyond all means, and, finally, a medically non-indicated immunosuppressive treatment to enforce HCMV reactivation for research purposes is a "do-not-even-think-about-it". Experimental animal studies, provided that they are properly designed to meet a clinical correlate, can make predictions and give proof of concept [8].

Back in 1994, these questions have in fact already been addressed in the mouse model of murine CMV (mCMV) infection by comparing infection of immunologically immature neonatal mice on day one post-partum with that of immunologically developed, young adult mice [9]. It is important in this context to note that the neuronal developmental stage of neonatal mice corresponds to that of human fetuses at the end of the second trimester, so that this can be viewed as a sort of mouse model of congenital HCMV infection [10]. Latent infection in both experimental groups was tested 1 year after primary infection, which is quite late in the lifespan of mice and thus qualifies as a model for latent infection of the elderly. At that late time, viral genomes were already cleared from bone marrow as well as from blood leukocytes, a stage that we today refer to as "canonical lifelong type-1 latency" in tissues/organs as opposed to "non-canonical transient type-2 latency" in cells of the hematopoietic lineage (see also the contributions by Reddehase and Lemmermann [4] and by Marandu and colleagues [11] in this issue of *MMIM*). Importantly, absence of viral genomes in blood leukocytes ensures that viral genomes detected in multiple organs reflect latency in tissues and not in cells circulating in the vasculature.

In essence, compared to infection of adult mice, "pseudo-congenital" infection of neonatal mice led to a prolonged multiple organ infection with an overall 100-fold higher virus production despite a 1000-fold lower initial virus dose that had to be used to avoid 100% lethality [9]. This high and prolonged virus production in the acute phase of infection led to a high titer of neutralizing antibodies as well as to high copy numbers of latent viral genomes in all organs

of all mice tested, which included spleen, lungs, salivary glands, heart, adrenal glands, and kidneys. In contrast, in the group of mice infected at adult age, productive infection was rapidly resolved, titers of neutralizing antibodies were lower, and latent viral genomes were undetectable in spleen and kidneys (6 of 6 mice tested) and rarely detected in salivary glands, heart, and adrenal glands (in each case in 1 mouse out of 6 mice tested). Only in the lungs could viral genomes be detected in all mice tested, which confirmed the lungs as being a major organ site of CMV latency in the mouse model [12].

Finally, when mice of the two groups were subjected to total-body γ-irradiation [9], the cumulative incidence of virus recurrence in salivary glands, spleen, and lungs in the "adult" group was 6.7% (2 reactivation events in any of these 3 organs in 30 mice tested), and in both cases infectious virus was found in the lungs, which is consistent with the higher latent genome burden in the lungs compared to other organs. In contrast, the cumulative incidence of virus recurrence in these three organs in the "neonatal" group was 86.7% (26 reactivation events in any of these three organs in 30 mice tested). Notably, recurrence events followed a random pattern of recurrence in a single organ or in combinations of two organs, and in one case out of 30 mice tested, recurrent virus was found in all three organs. There is strong evidence to propose that antiviral antibodies prevented an inter-organ spread of recurrent virus, so that recurrent virus remained confined to the organ(s) in which the event of reactivation had occurred in a stochastic fashion ([9], see also the contribution by Krmpotic et al. in this issue of MMIM [7]) (Fig. 1).

All in all, the murine model predicted that the risk of virus recurrence correlates with the tissue burden of latent virus genomes that is determined by the overall extent and duration of viral productivity during the past primary infection. Translated to humans, this predicts a high risk of recurrent infection when the primary infection had occurred peri- or postnatally, for instance, by breast feeding, and decreasing risks after primary infections at later times in life, such as virus transmission at day care center age or by sexual transmission at adult age. Unlike in experimental models, reality in human infection is further complicated by superinfections and episodes of recurrent infection that add to the burden of latent viral genomes.

Acquisition of HCMV by age

The question has persisted for 25 years if the findings in the mouse model discussed above provide a basis for multifocal HCMV latency and recurrence and if they provide

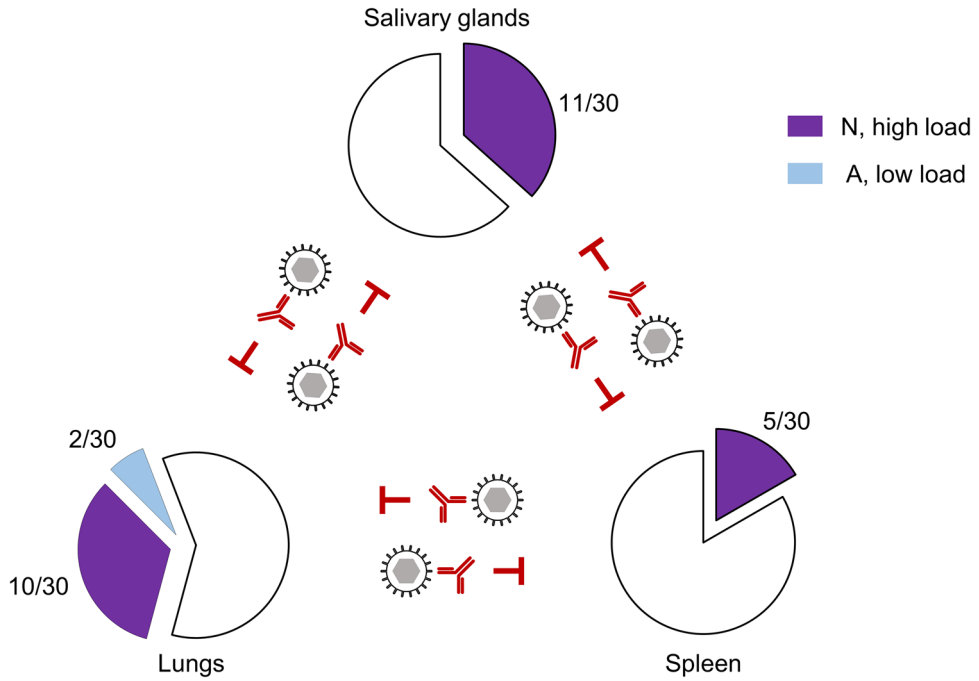

Fig. 1 Incidences of organ-confined stochastic virus recurrence and prevention of inter-organ virus spread. *N*, group of 30 BALB/c mice infected as neonates with 10^2 plaque-forming units of mCMV, carrying a high load of latent viral DNA in their organs. *A*, group of 30 BALB/c mice infected at adult age with 10^5 plaque-forming units of mCMV, carrying a low load of latent viral DNA in their organs. At 1 year post-infection, latent virus was reactivated by a sublethal dose of total-body γ-irradiation, and recurrence of infectious virus was monitored in salivary glands, lungs, and spleen. Pie charts symbolize recurrence incidences in the respective organs. Virus–antibody complexes symbolize prevention of virus spread between organs. The scheme is based on data from [9]

a rationale for the diversity of clinical manifestations and outcomes of human CMV disease. To address these questions, we review here an age-related acquisition of HCMV and the immune responses to HCMV in infants versus older children and adults.

At what age do humans naturally acquire HCMV? The natural route of HCMV acquisition is via breast milk [13]. Acquisitions via exposure to maternal mucosal cervical–vaginal secretions at birth and via child-to-child transmission in infancy also occur. Thus, in most developing countries and for most human populations, nearly 100% of individuals are HCMV seropositive by age 2–5 years.

In more developed countries, only about 33% of individuals are infected in the first 5–6 years of life [14]. Beyond the pre-school years, the rate of acquisition of HCMV based on acquisition of antibodies against the virus is about 2% per year [14]. Regardless of geographic location, most humans acquire an HCMV infection by 70 years of age. The major source of infection of older children and adults in developed countries is frequent exposure to children less than 3 years of age [15–19]. Although not formally proven, sexual transmission of HCMV also appears to be possible. However, in all studies of HCMV acquisition, exposure to young children has been an independent predictor of infection [20, 21]. In studies of transplant patients and those with AIDS between 50 and 100% are infected with HCMV before immunosuppression [22].

Immune responses to HCMV by age

Many studies have documented prolonged urinary and salivary shedding of HCMV in young children acquiring HCMV compared to a much shorter duration of viral shedding in adults and older children [23–25]. We confirmed this in one study of 13 young children by measuring HCMV DNA levels in urine using a real-time PCR assay and by viral culture [25]. Following HCMV acquisition, children, but not adults, persistently shed virus in urine, and this was observable for at least 29 month post-infection. All 13 children were positive by both assays. In contrast, HCMV was not detected by either assay in urine from any adult with past primary infection. To determine whether this result was typical for adults with recent primary HCMV infection, we retrospectively analyzed data on a group of 30 healthy women with documented primary HCMV infection and found that 90% of these subjects ceased urinary shedding by 6 months after acquisition of virus.

The fact that young children shed HCMV much longer than adults suggests a deficient immune response to HCMV among infants and young children. If so, this is probably virus induced, since it is to the virus's survival advantage to prolong viral shedding and enhance transmission during infancy and early childhood as compared to adulthood.

Following a primary infection with HCMV, infants and young children produce ample quantities of anti-CMV-IgG antibodies which persist for life [26, 27]. HCMV always establishes a persistent/latent infection with HCMV-specific CD8 T cells controlling viral replication. We investigated whether a developmental deficiency in antiviral CD8 T-cell-mediated immunity during childhood may contribute to prolonged viral shedding [28]. We observed that HCMV-specific CD8 T-cell responses in asymptomatic children with active infection and shedding virus were not different from adults with recent or long-term infection in frequency and functional analyses. High urine HCMV concentrations were detected in young children, even though HCMV-specific CD8 T-cell responses were normal and equivalent to adult levels. Thus, a prolonged primary HCMV infection in young children is not caused by a deficient HCMV-specific CD8 T-cell response. Because healthy children, unlike adults, continue to have local HCMV replication, CD8 T cells may function primarily to prevent symptomatic, disseminated disease but not to control viral shedding.

In another study, we observed that normal healthy immunocompetent young children after a recent primary HCMV infection produced far fewer HCMV-specific CD4 T cells that produced IFN-γ than did adults [25]. The differences in CD4 T-cell function persisted for more than 1 year after viral acquisition, and did not apply to CMV-specific IFN-γ production by CD8 T cells. The IFN-γ-producing CD4 T cells of children or adults that were reactive with HCMV antigens were mainly the $CCR7^{low}$ cell subset of memory ($CD45R0^{high}CD45RA^{low}$) cells. The decreased IFN-γ response to HCMV in children was selective, because their $CCR7^{low}$ memory CD4 T cells and those of adults produced similar levels of this cytokine after stimulation with staphylococcal enterotoxin B superantigen. CD4 T cells from children also had reduced HCMV-specific IL-2 and CD154 (CD40 ligand) expression, suggesting an early blockade in the differentiation of viral-specific CD4 T cells. Thus, CD4 T-cell-mediated immunity to HCMV in humans is age-dependent and is likely to control renal viral replication and urinary shedding.

Human and mouse data compared

It is interesting and reassuring that after 25 years, the mouse experiments of Reddehase et al. [9] are consistent with human observations. This includes prolonged viral shedding during infancy and prolonged viral shedding during reactivation of HCMV from multiple organs following immunosuppression. Thus, it is entirely plausible, even likely, that primary infections in infancy and childhood as compared to acquisition during late childhood and adulthood, lead to higher viral loads in more organs than occurs among those infected later in life. Final proof in humans is pending,

simply because no clinical studies were undertaken so far to relate the individuals' infection histories to the burden of latent virus in organs. Obvious hindrances for such clinical studies are the uncertainty regarding the precise time of primary infection in concert with the difficulty to take biopsies from multiple organs for determining latent viral DNA load. Intriguingly, the stochastic nature of virus recurrence observed in the mouse model may explain why some patients develop retinitis, others pneumonitis, others hepatitis, and still others nephritis after immune suppression. Again, there is of course no way in humans to test this hypothesis directly. For these reasons, animal models of human CMV, provided that they are well-designed to meet a clinical correlate (critically discussed in [8]) are likely to continue to enhance our understanding of pathogenesis of HCMV infections and aid in the design of antiviral interventions.

Outlook: is there a pediatric root of memory inflation?

Expansion of the pool of virus-specific CD8 T cells over time is a hallmark of CMV infections, a theme covered in this issue of *MMIM* by a couple of contributions. In the murine model, the hypothesis has been raised that a high number of latent viral genomes in tissue cells enhances the probability for desilencing events, which initiate reactivated viral gene expression that eventually leads to the presentation of antigenic viral peptides driving CD8 T-cell proliferation ([29, 30], reviewed in [31, 32]). Memory inflation associated with latent CMV infection is observed in humans too, in particular in the elderly (for the most recent review articles, see [33, 34] in this issue of *MMIM*). We find it worthwhile considering clinical studies trying to relate memory inflation to latent viral genome burden in tissues and the private histories of HCMV acquisition. Again, this will not be an easy venture due to all the limitations for clinical investigations already discussed above.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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