Congenital Cytomegalovirus Disease

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Abstract Of the myriad of congenitally and perinatally acquired infections that can impair the neurodevelopment of the infant, cytomegalovirus (CMV) is the most important. In the developed world, congenital CMV infection occurs in approximately 1 % of all pregnancies. Long-term neurodevelopmental disabilities include developmental delay, cerebral palsy, seizure disorders, and sensorineural hearing loss. This chapter summarizes the epidemiology and impact of congenital CMV on brain development. Hypotheses regarding the pathophysiology of CNS injury are reviewed. Prospects for intervention are also summarized.

Keywords Cytomegalovirus • Congenital cytomegalovirus infection • Cytomegalovirus vaccine • Cytomegalovirus neuropathogenesis • Sensorineural hearing loss • Inflammatory response • Cytomegalovirus immune evasion

1 Epidemiology of Congenital CMV Infection

Human cytomegalovirus (CMV) is a ubiquitous betaherpesvirus that replicates only in human cells. CMV infections are generally asymptomatic in immunocompetent individuals but produce a mononucleosis syndrome (heterophile negative) in approximately 10 % of primary infections in older children and adults [1–3]. Similar to other herpesviruses, CMV becomes latent after primary infection, but it may reactivate from latency, particularly in the setting of immune suppression, leading to disease in HIV-infected patients [4], or in solid organ or hematopoietic stem cell

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transplant patients [5, 6]. Acquisition of infection typically requires intimate contact with body fluids (blood, urine, saliva, breast milk). There is no seasonality to infection. Patient populations with increased rates of primary infection include breastfeeding infants, sexually active adolescents, and childcare providers in group day care [7–13]. Seroprevalence is higher among nonwhites and among individuals of lower socioeconomic status [14].

From a public health perspective, the most important medical impact of CMV is the damage caused to the developing central nervous system (CNS) of a fetus when infection occurs in utero. A recent meta-analysis of published studies concluded that the overall birth prevalence of congenital CMV infection was approximately 0.65 %, although this study also noted that congenital infection rates varied considerably among different study populations [15]. This corresponds to over 60,000 congenital infections annually in the United States and Europe. Some of the risk factors for congenital CMV infection include nonwhite race, low socioeconomic status, premature birth, and neonatal intensive care unit admittance. The risk of fetal transmission appears to increase with gestational age, but neurological outcomes are more severe when infection occurs during the first trimester [16, 17]. However, viral transmission can occur during the entire gestation period, and adverse neurological outcomes may still be observed in the setting of infections acquired in late gestation [18], although CNS injury is much less common when fetal infections are acquired during this time point in pregnancy [19].

The prevalence of congenital CMV infection within a given population correlates directly with maternal CMV seroprevalence [20]. Indeed, preconception immunity to CMV does not confer complete protection against fetal transmission in subsequent pregnancies, although the risk of congenital CMV clearly is greater in the setting of a primary infection during pregnancy. Overall, transplacental transmission of virus occurs in about one-third of mothers with primary CMV infection [21–23], and approximately one-half of these infections acquired in utero result in a symptomatic clinical syndrome [24]. Fetal infection occurs in up to ~1.5 % of pregnancies in which there is preconception immunity [15], either due to reactivation of latent infection or, probably more commonly, due to maternal reinfection with novel strain variants of CMV [21, 25, 26]. Strain variation among clinical isolates of CMV is substantial, and the presence of preexisting maternal immunity does not appear to fully protect against different strains [27–29]. Importantly, preconception maternal immunity unfortunately does not completely protect the infected fetus from neurological injury and sequelae [30]. Indeed, in a study of 300 children with confirmed congenital CMV, investigators at the University of Alabama, Birmingham, found that the incidence of progressive hearing loss was not different in children born to mothers with preexisting immunity when compared to women who gave birth to infected newborns in the setting of a primary maternal infection during pregnancy [31]. Such observations complicate the conceptualization and design of a preventative CMV vaccine (reviewed later in this chapter). These observations suggest that infection prevention strategies should not only be targeted to seronegative but also to seropositive pregnant women.

Congenital CMV infection is the major infectious cause of birth defects and childhood neurodevelopmental disorders. Among the primary clinical manifestations associated with congenital CMV infection, the most devastating are those involving the developing CNS since, in contrast to other end-organ injury, CNS injury is generally believed to be irreversible. The presence of symptoms at birth in an infant with congenital CMV is an important harbinger of brain involvement and potential neurodevelopment sequelae. CNS injury and attendant long-term neurodevelopmental deficits are substantially more common in infants with symptoms at birth. The most commonly observed symptoms of CMV infection at birth are intrauterine growth retardation (IUGR), purpura, jaundice, hepatosplenomegaly, microcephaly, hearing impairment, and thrombocytopenia [32]. While clinical signs due to abnormalities of the reticuloendothelial system (like anemia, hepatosplenomegaly, jaundice) are transient, neurological deficits either are evident at birth and typically persist for life or tend to become evident (as sensorineural hearing loss) in early childhood. Only 10–15 % of children with congenital CMV infection exhibit clinical signs at birth, although even children who appear asymptomatic at birth are at risk for neurodevelopmental sequelae [33]. Most children (60–90 %) with symptomatic infection, and 10–15 % of those with asymptomatic infection, develop one or more long-term neurological sequelae, such as mental retardation, psychomotor retardation, cerebral palsy, developmental delay, sensorineural hearing loss, and ophthalmologic abnormalities [32, 34, 35]. Current estimates indicate that approximately 8,000 children in the United States are affected each year with one or more neurological sequelae related to in utero acquisition of CMV infection. CMV exerts a far greater impact on neurodevelopmental outcomes than that of other, better-known childhood disorders, such as Down syndrome (4,000/year), fetal alcohol syndrome (5,000/year), or spina bifida (3,500/year), although public awareness of CMV remains low [36–38]. In light of the public health significance of CMV-related long-term neurological disabilities, increased attention needs to be devoted to the study of the neuropathogenesis of this infection. Accordingly, the development of effective interventions, such as vaccines, would have a substantial and major public health impact on the prevalence of childhood disabilities [39].

2 Pathogenesis of CNS Injury Induced by Congenital CMV

Given the intrinsic limitations of performing histopathological studies on brain tissue from infants with symptomatic congenital CMV infection, the pathogenesis of CNS injury must be indirectly investigated. Brain imaging studies, cell culture models of infection, and observations from the study of cytokine and host inflammatory responses in children with CMV-induced brain injury (including cerebral palsy) have provided insights into the pathogenesis of CNS injury. In addition, animal models of perinatal and congenital CMV infection have provided important additional information about mechanisms of pathogenesis. These studies are considered in this section of the review.

2.1 Imaging Studies

A number of imaging modalities have contributed to our understanding of the natural history and pathogenesis of congenital CMV. Of particular interest are the imaging studies that have been reported of the developing brain in the CMV-infected fetus. Serial ultrasonograms or cranial CT scans have proven useful in detecting the overt pathological alterations in the fetal brain of symptomatic children and can accurately predict development of cognitive and motor deficiencies [40–42]. Importantly, the absence of detectable lesions in an asymptomatic congenitally infected newborn does not provide complete reassurance against the eventual diagnosis of CNS injury, since infants with normal CNS imaging are nevertheless at risk for developing hearing loss later in life [41].

Fetal imaging studies can demonstrate structural brain abnormalities as early as 28 weeks of gestation, using either MR images or ultrasonograms. T2- and T1-weighted MRI scans of CMV-infected fetal brains have demonstrated white matter abnormalities reflective of acute responses to infection, such as the loss of intermediate zone layer, focal necrosis, and hemorrhage. Chronic lesions due to CMV infection can also be demonstrated, including ventricular dilatation, white matter gliosis, atrophy (volume loss), parenchymal cysts, ependymal cysts, calcifications, and cortical malformations, most notably polymicrogyria [43]. Fetal sonographic studies obtained between 22 and 37 weeks of gestation have also demonstrated structural brain changes attributable to CMV. Transvaginal ultrasonograms have been reported to show abnormal periventricular hyper-/hypoechogenicity, ventricular adhesions, cystic formation around the ventricles, ependymal protrusions, abnormal sulci formation, and hypoplasia of the corpus callosum [44]. Fetal imaging studies have been useful for establishing timelines for determining the embryologic sequence of CNS infection, and these findings may in turn be useful in predicting neurodevelopmental prognosis [45]. Lanari and colleagues recently compiled an elegant summary of the pattern of neurodevelopmental injury as a function of timing of acquisition of brain infection in utero. This review noted that lesions occurring prior to 18 weeks gestational age commonly include lissencephaly with thin cerebral cortex, cerebellar hypoplasia, ventriculomegaly, periventricular calcification, and delay in myelination. At 18–24 weeks, migrational abnormalities may occur, including polymicrogyria, schizencephaly, and periventricular cysts. Third trimester infections may be associated with central nervous system (CNS) lesions that may include delayed myelination, dysmyelination, calcification, and white matter disease [46].

Neonatal imaging of children with symptomatic CMV infection is typically associated with structural brain abnormalities similar to those described in the infected fetus. The most frequent of these is the presence of intracranial calcifications, present in approximately 70 % of cases [47]. Abnormal cranial ultrasonograms (demonstrating periventricular or parenchymal calcifications, or increased ventricular size) can be performed in the neonatal period in symptomatic congenitally infected infants and are able to both identify children with overt, acute CNS

injury as well as those at risk for later neurological deficits [41]. Ultrasonography, however, may miss more subtle CNS pathology in the neonate. Brain MRI of children with congenital CMV has revealed multiple intracranial pathologies, including white matter lesions, neuronal migration, and myelination abnormalities; polymicrogyria; cerebellar, cortical, and hippocampal dysplasia or hypoplasia; periventricular cysts; and ventriculomegaly [48, 49]. The finding of subtle white matter lesions with or without polymicrogyria and in combination with anterior temporal lobe cysts was described in a study of congenital CMV identified by PCR-based screening of Guthrie newborn screening cards [50]. Another recently reported study assessed the diagnostic and prognostic value of cerebral MRI in comparison to ultrasonography in predicting neurodevelopmental outcome in newborns with congenital CMV. Of note, MRI provided additional information beyond that which could be identified by ultrasound (white matter abnormalities in three cases, lissencephaly/polymicrogyria in one and a cyst of the temporal lobe in another one) in four infants who had abnormal findings in both exams. Even more significantly, three newborns had normal ultrasound exams, but had abnormal MRI exams documenting white matter abnormalities and, in one case, cerebellar hypoplasia [51]. Further studies will be required to identify the prognostic role of MRI, particularly with respect to the finding of white matter lesions currently not identifiable by ultrasonography. Figure 1 demonstrates an example of CNS pathology in an infant with symptomatic congenital CMV infection.

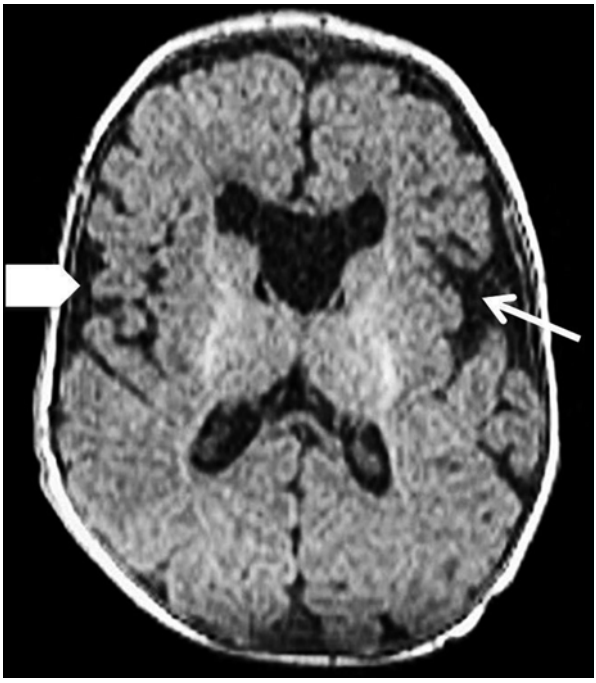

Fig. 1 T1-weighted brain MRI of infant with congenital CMV infection. Axial view is demonstrated. Findings include ventriculomegaly, loss of brain volume with prominence of sulci (*arrow*), pachygyria (*solid arrowhead*) on the surface, and very thin cortex. This infant went on to manifest a seizure disorder and profound neurodevelopmental delay

2.2 Cell Culture Models of CMV Infection

Although the developing brain is the major target for end-organ damage in the setting of congenital CMV infection, the precise cellular targets of infection remain incompletely characterized. Inclusion bodies in the brain have been detected during postmortem histological analysis of fatal cases of congenital CMV infection [52], but little or no histological data identifying the different cell types infected during congenital CMV infection has been reported. Cell culture models of human brain cells are therefore vital in attempting to elucidate the pathogenesis of fetal CNS injury. Both primary human cell culture systems and studies with brain-derived cell lines have demonstrated that practically all cell types in the brain have some degree of susceptibility to CMV infection. The current state of knowledge about CNS targets of infection, including the permissiveness of various cell types for full viral replication and the putative mediators of injury, is summarized in Table 1. Brain microvascular endothelial cells [53–55], astrocytes [56], neuronal cells [57], oligodendroglial cells [58], microglia/macrophages [59], and neural progenitor/stem cells (NPCs) [60] all have a propensity for CMV infection. However, these different cell types vary in their ability to support a complete viral replication cycle, with the permissivity of any given cell type for completion of the viral infection cycle limited by host and viral transcription factors and other elements regulating viral gene expression [47].

Of the cell types of the brain that can be infected with CMV, the astrocyte, the major cell type constituting about 70 % the brain, is the cell type most supportive of productive CMV replication. Primary human fetal astrocyte cultures support cytopathic viral replication, immediate early (IE) gene expression, and β-promoter (early gene) activity, and infectious virus is readily detectable in cell supernatants [56]. Notably, these cells, in association with brain microvasculature endothelial cells (BMVEC), form the blood–brain barrier, a structure that maintains the highly regulated solute, immunologic, and cellular microenvironment in the CNS [61]. Lytic viral replication is supported by BMVEC, which in turn promotes monocyte activation, migration, and infection in the CNS [62].

In contrast to astrocytes, primary differentiated human neurons have generally been found to be refractory to CMV replication, with some exceptions as noted below. Highly purified primary neuronal cultures (>90 % neurons) contain a small percentage of dividing astrocytes that support viral replication, but viral gene products cannot be detected in neurons [56]. The block in the viral replicative cycle appears to be at the level of the major immediate early promoter (MIEP), and not due to a defect in viral entry [60]. Experiments with undifferentiated human oligodendroglioma (HOG) cells, representative of immature oligodendrocytes, demonstrate that oligodendrocytes, like neurons, may not be fully permissive for CMV infection. However, CMV IE, US11, and glycoprotein B (gB) gene expression is induced in HOG cells upon differentiation with phorbol-myristate acetate (PMA), without production of viral progeny [58]. Some studies utilizing neural progenitor cells (NPCs) have demonstrated, following in vitro differentiation and enrichment, that neurons can support productive replication of CMV [63, 64]. Taken together, it appears that the state of cell differentiation as well as its functional status may modulate permissiveness

Table 1 CNS targets of CMV infection and pathogenic mechanisms. Impact of CMV infection on major cell types in the developing fetal CNS is summarized, and potential mechanisms mediating neuropathogenesis are noted

Cell type	Permissivity for infection	Cytokines and inflammatory mediators induced	Potential role(s) in neuropathogenesis
Astrocytes	Fully permissive for lytic replication	Predominant cytokine produced in infected astrocytes is TGF-β; CCL2, CXCL8, CCL3, and CCL5 are also produced	Plays key role in intercellular signaling and neuronal development; modulates synaptic activity within the nervous system; astrocyte signaling plays key role in microglial activation
Microvascular endothelial cells (BMVEC)	Fully permissive for lytic replication	Key cells in promoting spread; possible site of *trans*-endothelial entry of CMV into the brain	BMVEC participate in formation of blood–brain barrier (BBB); infection promotes monocyte activation, migration, infection
Pericytes	Fully permissive for lytic replication	CXCL8/IL-8, CXCL11/ITAC, CCL5/RANTES, TNF-α, IL-1β, and IL-6	Support BMVEC cells; contribute to BBB; infection contributes both to viral dissemination in CNS and neuroinflammation
Microglia	Abortive; not permissive for lytic replication	Respond to CMV by producing TNF-α, IL-6, CXCL10, CCL2, CCL3, CCL5	Reservoir for latent genome; origin from myeloid precursors; activation may play role in perturbation of neural cell development, oligodendrocyte maturation
Neural progenitor/stem cells (NPCs)	Fully permissive for lytic replication	CMV interferes with migration, proliferation, and differentiation into neurons and astrocytes; modifies cell cycle; modifies metabolism	Disruption of normal cellular processes of NPCs by CMV may be responsible for most structural and migratory abnormalities seen during congenital infection
Neurons	Uncertain; minimal evidence for permissive infection	Block in replication at level of immediate early transcriptional machinery; virus enters but does not complete life cycle	NPCs can be induced to undergo differentiation in cell culture, and under these conditions neurons may support productive viral replication

of neurons and oligodendrocytes to CMV brain infection in cell culture systems. The implications for in utero neuropathogenesis remain to be elucidated.

Microglia, the end-differentiated resident brain macrophages, also do not appear to support productive CMV infection [56]. However, CMV DNA has been demonstrated in infected microglial cells in the absence of detectable viral IE proteins [65, 66]. It has been proposed that brain microglia are replenished from bone marrow-derived

precursors that migrate into the brain [47]. It has been suggested that myeloid precursor cells may be a site for CMV latency and a vehicle of viral dissemination in the host [67–70]. Although myeloid precursors and monocytes are not typically productively infected by CMV [70], they support productive CMV infection at certain stages of differentiation [71]. In addition, endothelial cell-adapted viral strains have been shown to infect both macrophages and dendritic cells [72], a process which requires the CMV gene products essential for endothelial tropism, UL128, 130, and 131 [73]. These gene products have recently emerged as key candidates for CMV subunit vaccines [74]. It has been suggested that macrophages originating in the vascular space may be an important vehicle for trafficking of virus into the CNS in the developing fetal brain [47].

NPCs have emerged as cells of particular interest in the pathogenesis of congenital CMV-induced brain injury. These cells are predominantly located in the subventricular zone and subgranular zone of the hippocampus in the mammalian brain [47]. NPCs possess the ability to migrate, proliferate, and differentiate into neurons, astrocytes, and oligodendrocytes. Figure 2 provides a schematic model of the central role of these cells in CMV-induced neuropathogenesis. In the setting of CMV brain infection (including histopathological observations discerned from fatal congenital infections), it is well recognized that virus preferentially infects cells in the ventricular or subventricular regions [52, 75]. This anatomic distribution suggests the possibility that CMV replication may be particularly well adapted to replicate in the neural stem/precursor cells residing in this region. Several studies have demonstrated that human CMV replicates efficiently in undifferentiated human neural precursor cells in cell culture [60, 63, 64, 76, 77]. It has been proposed that the extent to which these cells are infected in utero may determine the outcome of CNS sequelae associated with congenital CMV infection [47].

CMV infection of human neural precursor cells appears to inhibit their differentiation into both neurons and astrocytes, an effect that may be mediated by virus-induced apoptosis in cells undergoing differentiation [76–78]. It has been proposed that CMV replication may inhibit neural precursor cell proliferation by altering cell cycle mechanisms [60, 79] and may perturb expression of genes related to neuronal metabolism and neuronal differentiation in NPCs [78]. Indeed, disruption of these cellular processes in neural precursor cells may account for a large portion of the structural and migratory abnormalities seen during congenital human CMV brain infection [47, 78]. A recent study in a cell culture model suggests that this susceptibility does not diminish with advancing brain development. In this study, NPC cultures derived at different gestational ages were evaluated after short (3–6) or extended (11–20) in vitro passage for viral entry efficiency, viral gene expression, virus-induced cytopathic effect, and release of progeny virus. Extended passage cultures showed evidence of increased viral entry and more efficient production of infectious progeny, suggesting that CMV infection in fetal brain may continue to result in neural cell loss even with advancing brain development [80]. These observations suggest that persistent CMV infection may continue to negatively impact brain development postnatally. Extended, long-term infect of NPCs postnatally pro-

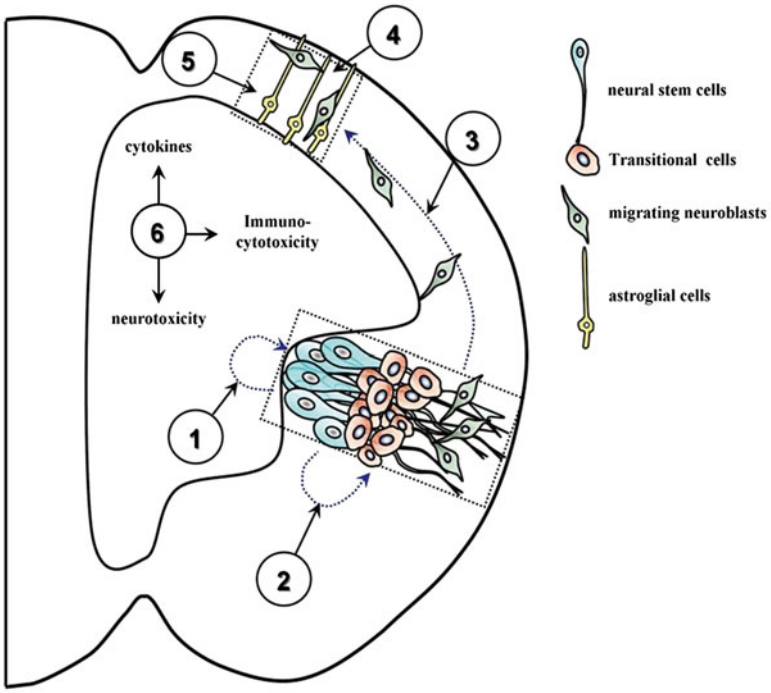

Fig. 2 Schematic representation of mechanisms of brain injury following infection with CMV. Neural stem cells (in *blue*), found along the lateral ventricular wall of the brain, are involved in the development of new neural circuits in the developing brain. These cells differentiate into new brain cells (astrocytes, oligodendrocytes, and neurons), either directly or via an intermediate transitional progenitor cell (*red cells*). Formation of new neural circuitry involves migration of neuroblasts (*green cells*), through a directed pathway that is supported in part by astroglial cells. CMV may potentially affect any or all of these stages: (*1*) Infection of neural stem cells may disrupt their ability to maintain a self-renewing cycle; (*2*) Differentiation of neural stem cells via the transitional cells and eventually neuroblasts may also be disrupted by CMV; (*3*) Brain infection affects the migratory patterns of neuroblasts, particularly during cortical and cerebellar development; (*4*) This presumably alters the migratory patterning of other specific brain structures, causing improper layering of the neocortex; (*5*) Since glial cells are also susceptible to CMV, functions of glia in directing neuronal layering patterns may be affected. (*6*) Finally, infection can induce a myriad of inflammatory mediators, including cytokines and chemokines, and elicit inflammatory cell infiltration. *Reproduced from* Cheeran et al., Neuropathogenesis of congenital CMV infection: Disease mechanisms and prospects for intervention. Clin Micro Rev 2009: 22, 99–126

vides a mechanism by which CMV could to continue to exert an impact on neurodevelopmental processes in early childhood in the context of congenital infection of the CNS. This aspect of CMV replication in NPCs provides reinforcement for clinical trials examining the impact of extended, long-term (6 months) valganciclovir therapy in infants with congenital CMV infection [81].

2.3 Role of Inflammatory Response

In addition to the direct damage to specific cell types conferred by fetal brain infection with CMV, the inflammatory response to infection also is also increasingly becoming recognized as a major contributing factor in the pathogenesis of brain injury. Autopsies of prenatally infected fetuses with CMV have confirmed the presence of a significant inflammatory response in addition to viral inclusions in the brain [82–86]. Upon autopsy, one study recently found that nearly all fetal organs infected with CMV had evidence of inflammatory infiltrate and found that the level of organ damage was associated with the level of inflammation; intriguingly, in addition to the damaging direct effects of viral brain infection and the attendant inflammatory response, hypoxic brain injury due to severe CMV placentitis was also postulated as a contributing factor in brain injury [83]. Tissue-specific viral load has been proposed to impact the magnitude of the inflammatory response. In one study, it was noted that tissue viral load was correlated to immune response; low CMV viral load elicited only a modest immune response with mild brain damage, while tissue containing high viral load had high levels of cytotoxic CD8+ T-lymphocytes, which are associated with immune-related structural damage [82]. In total, this evidence suggests that direct fetal infection with a neurotropic pathogen like CMV not only increases the risk of neurological sequelae mediated by factors such as lytic infection, disruption of neuronal migration, and increased apoptosis, but also through a cascade of events triggering a pathological fetal immune response.

A current view of mechanisms of neuroinflammation in adults revolves around the concept of "reactive microgliosis" [87]. Microglia can be activated in several different patterns, including classical activation (M1 phenotype), alternate activation (M2a phenotype), or acquired deactivation (M2b phenotype) [88, 89]. While the M1 phenotype appears to promote a deleterious, pro-inflammatory status, it has been proposed that the M2 phenotype could favor brain repair [90, 91]. In addition to promoting a pro-inflammatory milieu, developmental brain damage mechanisms can also be driven by microglial activation [92–95]. Systemic and brain inflammation driven by activated microglia in turn impacts the development of different neural cell populations, and influences oligodendrocyte maturation [96] and survival [97, 98]. CMV-driven release of cytokines, particularly IL-6, could impact proliferation and function of neural stem cells [99]. Migrating neurons can be compromised by the release of inflammatory factors released by activated microglia, potentially leading to neuronal cell death or abnormal neuronal migration, one of the hallmarks of CMV infection of the developing fetal brain [100].

A number of studies have attempted to define the precise cytokine responses associated with fetal brain infection with CMV, predominately using cell culture models. In one model of cultured human glial cells, derived from 16- to 20-week-old fetal brain tissue, response to CMV infection is heralded by expression of a number of immune mediators, including chemokines and cytokines [101]. Microglial cells respond to CMV infection by producing TNF-α and IL-6 as well as CXCL10, CCL2, CCL3, and CCL5 [102, 103]. Many of the cytokine responses of microglial cells appear to be driven by innate responses mediated by pattern

recognition receptors on microglia that recognize pathogen-associated molecular patterns [104]; for CMV, these ligands appear to be envelope glycoproteins gB and gH, which signal through Toll-like receptor (TLR) 2, and double-stranded RNA molecules generated during infection, which signal via TLR3 [105–109]. Chemokines and cytokines are also elicited by CMV infection of astrocytes. As noted, the chemokine response in astrocytes includes CCL2, CXCL8, CCL3, and CCL5 [102, 103]. In contrast, the cytokine response to CMV in astrocytes appears to be restricted to TGF-β, an anti-inflammatory cytokine [110]. Primary brain vascular pericytes have recently been shown to be a source of cytokine production in the context of CMV infection, including CXCL8/IL-8, CXCL11/ITAC, CCL5/RANTES, TNF-α, IL-1β, and IL-6 [111].

In addition to inducing the production of chemokines and cytokines following CMV infection of the fetal brain, the viral genome itself encodes homologs of several immunomodulatory proteins, including homologs of CXC (*UL146*, *147*) and CC (*UL128*) chemokines [112]. CMV also encodes functional homologs of chemokine receptor-like G-protein coupled receptors [113]. The role that such gene products play in the pathogenesis of fetal brain injury is unknown. CMV also encodes a functional homolog of the IL-10 gene. Transcription of this gene product has been shown to inhibit CXCL10 production in human microglial cells, a possible mechanism by which CMV genes contribute to evasion of host immune clearance [102].

3 CMV Fetal/Neonatal Brain Infection: Prospects for Intervention

Currently, there are limited interventions for the treatment and prevention of fetal and neonatal CMV brain infections. In women with primary CMV infections complicated by intrauterine transmission, the use of an anti-CMV high-titer immunoglobulin (HIG) has been associated with improved neurodevelopmental outcomes, including regression of fetal cerebral abnormalities for fetuses treated in utero [114, 115], although these studies are uncontrolled and proof of efficacy is still uncertain. A controlled, multicenter trial of ganciclovir in infants with congenital CMV infection and neurological findings at birth indicated that 6 weeks of intravenous therapy was associated with improved short-term and long-term audiologic outcomes [116]. In a follow-up study in which infants were administered serial neurodevelopmental screening examinations, ganciclovir therapy was associated with fewer developmental delays at 6 and 12 months, compared with untreated infants [117]. Based on these encouraging observations, a trial is currently being conducted that will compare 6 weeks to 6 months of therapy, using oral valganciclovir [81], toward the goal of ascertaining whether any additional neurodevelopmental benefit might be realized by longer treatment courses.

Ultimately, the best prospects for control of congenital CMV rest with the development of an effective preconception vaccine. Several candidate vaccines are in various stages of preclinical development, and some have advanced to clinical trials [118, 119]. Most vaccines currently being examined in human studies target envelope

glycoprotein B (gB) and various combinations of T-cell targets, including the pp65 (ppUL83) tegument protein and the major immediate early gene product-1 (IE1) [120]. The gB vaccine has demonstrated modest efficacy in a phase II study in young women of child-bearing age [121]. As previously noted, vaccine development has been complicated by the increasing recognition that women can become reinfected with new, novel strains of CMV during pregnancy and that these strains, in turn, can be transmitted to the fetus, resulting in attendant neurological injury and long-term sequelae [25, 122]. Ultimately, development of a CMV vaccine would therefore probably need to focus not only on prevention against primary infection in seronegative women, but also reinfection in seropositive women, in order to fully protect all infants against the neurodevelopmental sequelae of congenital infection.

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