Cmv infection epidemiology and pathogenesis

Virus Strain Variation”

An important variable that may impact the prognosis of infection may be viral strain variation. It has been hypothesized that some clinical strains of CMV are intrinsically more harmful, based on variability in genes implicated in viral pathogenesis. Some subtypes of CMV classified on the basis of their UL144 (TNF receptor homolog) sequence were described as being more likely to be associated with symptomatic disease(Arav-Boger *et al* ., 2006), irrespective of the viral load. On the other hand, other studies were unable to confirm any association with UL144 genotype and the outcome of infection. No differences in clinical outcome could be attributed to variants of the CK homologs, UL146 and UL147(Heo *et al* ., 2008).

When genotypes based on the sequence heterogeneity in the envelope glycoprotein gene, gN (UL73), were compared, congenital infection with one genotype, gN-1, was associated with an improved prognosis with respect to long-term neurodevelopmental sequelae(Pignatelli *et al* ., 2003). In another study of infants with congenital infection, the distribution of genotypes for the gB glycoprotein gene (UL55) showed significant differences, depending upon the disease classification observed, but no information was reported on long-term neurodevelopmental sequelae(Jin *et al* ., 2007).

Differences in virulence between strains of HCMV may reflect their abilities to attach to cells. HCMV strains Toledo (low passage in cell culture), Towne and AD169 (cell culture-adapted) exhibited differences in virulence in vaccinated volunteers. Growth differences relative to virulence of the various HCMV isolates have also been observed in endothelial cells. Differences in

glycoproteins may be the reason for the differences in abilities to attach and replicate in cells. HCMV was originally classified into four genotypes of gB, each with a characteristic nucleotide and peptide sequence, but later, a fifth glycoprotein genotype has been identified(Sweet, 1999).

Clinical HCMV isolates are slower growing on human fibroblast cells and differ from laboratory adapted strains of HCMV in that they encode additional sequences in the ULb' locus (about 19kb), which is believed to be associated with viral pathogenicity and/or the ability of the virus to grow on epithelial/endothelial cells(Hahn *et al* ., 2004). This locus is rapidly mutated and deleted in the process of adaptation of the virus to tissue culture fibroblast cells(Dargan *et al* ., 2010). The UL128-131 genes in the ULb' locus have been demonstrated to be necessary for virus entry into epithelial and endothelial cells by a newly identified endocytic method of cell entry that is different from the pathway of infection in fibroblast cells(Ryckman *et al* ., 2006).

Epidemiology

Human CMV is an ancient virus that is ubiquitous in human populations, reaching a prevalence of 100% in Africa and Asia, and approximately 80% in Europe and the USA, depending on socioeconomic status(Cannon *et al* ., 2010).

CMV infection is widespread and occurs worldwide.(Bate *et al* ., 2010). Seroprevalence rates vary depending on age (higher rates are observed among older persons), geography (higher rates in developing countries), and socioeconomic status (higher rates in economically depressed regions)(Bate

et al ., 2010, and Cannon *et al* ., 2010). Primary CMV infection occurs most commonly during the first 2 decades of life(Joseph *et al* ., 2006).

Non-white race, low socio-economic status, premature birth, and neonatal intensive care unit admittance are among the important risk factors for congenital CMV infection(Kenneson and Cannon, 2007). Congenital CMV infection can occur in 0. 5-2% of all pregnancies, often with devastating consequences for the developing fetus(SungandSchleiss, 2010). Among congenitally infected infants, approximately 10% have signs and symptoms of disease at birth. Although the remaining 90% of infants are asymptomatic at birth, 10-15% will subsequently develop permanent sequelae, including sensorineural hearing loss and mental retardation(Cheeran *et al* ., 2009). It has been reported that 25% of congenitally infected infants whose mother had a primary HCMV infection during pregnancy had at least one sequela, compared with 8% in infants born to women with recurrent infection(SungandSchleiss, 2010). The impact of congenital CMV is greater in the developed world because of the number of CMV negative women of child bearing age and the risk of primary infection during pregnancy which substantially increases the likelihood of congenital infection(Colugnati *et al* ., 2007). In the developed world, congenital HCMV is the second most common cause of mental retardation next to Down’s syndrome(Dollard *et al* ., 2007). Additionally, HCMV related deafness occurs at a greater frequency than that related to Hemophilus influenza infection in the preHIB vaccine era(McGregorandChoi, 2015).

Transplacental transmission of virus occurs in about one-third of mothers with primary CMV infection(Kenneson and Cannon, 2007), and approximately

one-half of these infections in utero result in a symptomatic clinical syndrome(Adler *et al* ., 2007). Epidemiological data suggest that the timing of acquisition of primary infection relative to the establishment of pregnancy is an important factor in establishing the risk to the fetus for in utero transmission(Revello et *al* ., 2006).

The infection is acquired by 40% of children within the first decade of life. Seroprevalence increases to 80% by the age of 60(Kenneson and Cannon, 2007).

Most HIV-infected individuals are seropositive for CMV. HIV infection accelerates the development of CMV-dependant immunological abnormalities(Barrett *et al* ., 2012).

In Africa, the prevalence of CMV IgG among HIV-negative adults was 81. 8% (range 55-97%). For HIV-infected adults the pooled CMV IgG seroprevalence was lower among those with clinically defined AIDS (81. 9%, range 59-100%) than among asymptomatic HIV-infected adults (94. 8%, range 71-100%), consistent with the notion of weaker humoral responses associated with AIDS progression. It is also possible that some non-HIV infected adults are infected but do not mount a measurable IgG response. Among pregnant women seroprevalence mirrored that among healthy blood donors, although the HIV status of participants was not always stated. In children, pooled seroprevalence was 88. 1% (range 80-100%). With this very high seroprevalence in children, even in very young infants, one would expect seroprevalence among adults to be consistently close to 100% (BatesandBrantsaeter, 2016).

In Egypt, the seroprevalence of CMV infection among pregnant women and acute lymphoblastic leukaemic patients was 100%(BatesandBrantsaeter, 2016).

Pathogenesis

CMV employs at least two distinct, cell-type specific mechanisms of cell entry. Entry of CMV into endothelial and epithelial cells is mediated by endocytosis in a pH-dependent fashion; in contrast, entry into fibroblasts is non-endocytic, and pH-independent. CMV fibroblast entry is believed to be initiated by binding of virion-associated gB to a cell surface receptor, followed by fusion with the cell membrane in a process that requires a complex of three other glycoproteins: gH, gL, and gO(Ryckman *et al* ., 2006). In contrast to the model of CMV entry for fibroblasts, endocytic entry of CMV into endothelial and epithelial cells requires a complex of gH, gL, and three other proteins encoded by a region of the CMV genome referred to as the UL128-131 gene locus(Wang and Shenk, 2005).

The pathologic effect of a CMV-encoded gene is believed to be mediated directly by that gene product; in other situations, CMV infection leads to downstream effects on cellular gene expression that then may potentially lead to pathologic outcomes. In many circumstances, CMV gene products mediate more than one pathogenic effect and there is considerable overlap across these categories(Schleiss, 2011).

Following infection, the messenger ribonucleic acid (mRNA) for the major 72-kilodalton IE protein is transcribed more abundantly than any other mRNA as a result of an upstream regulatory sequence of DNA that competes more

efficiently for ribonucleic acid polymerase 11(Stinski, 1984). These upstream enhancer sequences constitute the first step in the regulation of CMV gene expression. The 72-kilodalton protein is then transported back to the nucleus, presumably to influence the switch from restricted transcription of the long unique sequence to more extensive transcription. A block in the synthesis of IE proteins disrupts any further transcription of the viral genome, suggesting that these proteins may play a major role in determining whether a CMV infection is latent, persistent, or productive(Spector and Spector, 1984).

The pathogenesis of disease associated with acute CMV infection has been attributed to lytic virus replication, with end-organ damage occurring either secondary to virus-mediated cell death or from pathologic host immune responses targeting virus-infected cells(Britt *et al* ., 2008).