INTRODUCTION

منسّق:لون الخط: أسود
منسّق:تباعد الأسطر: تام 42 نقطة

Cytomegalovirus (CMV) belongs to the family of human herpe viruses. It is also known as the human herpes virus 5 (HHV-5). In immunocompromised host it becomes significant pathogen, causing the spectrum of different symptoms and affecting different tissues and organs Epidemiologic forms of CMV infection include primary infection reactivation or secondary infection, and superinfection or reinfection ***(Basić-Jukić ~~et al.,~~ et al., 2008).***

منسّق:لون الخط: أسود
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The risk of CMV disease is highest in seronegative recipients (R−) o seropositive donors (D+), and in patients who are heavily immunosuppressed such as those receiving antilymphocyte antibody therapy as induction or fo treatment of rejection ***(Opelz ~~et al.,~~ et al., 2004).***

منسّق:لون الخط: أسود

Pharmacologically-induced immunological dysfunction is especially severe when lymphocyte-depleting drugs such as muromonab-CD3 (OKT3 and anti-thymocyte globulin are used. Use of the anti-CD52 alemtuzumab which causes a prolonged suppression of T cell function, is particularly associated with higher risk of CMV disease, especially when it is used for the treatment of acute rejection. Acute rejection by itself is also associated with increased risk of CMV disease ***(Razonable, 2010).***

Viral factors, such as peak viral load or the kinetics of viral replication may influence the risk of CMV disease. A patient with a higher absolute viral load or a rapidly increasing viral load is at increased risk of CMV disease ***(Razonable ~~et al.,~~ et al., 2003).***

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منسّق:علامات الجدولة: 7.2 سم، يسار + ليس عند 52.8 سم + 15.61 سم

CMV infection has direct and indirect effects. Direct effects occur a the time of highest viraemia with severe clinical presentation. To the contrast indirect effects occur at the time of asymptomatic viraemia as th consequence of immunologic response. Indirect effects are mediated by cytokines, chemokines and growth factors ***(Basić-Jukić ~~et al.,~~ et al., 2008).***

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Direct effects include bone marrow suppression, pneumonia myocarditis, encephalitis, hepatitis, nephritis, cystitis, retinitis, enteritis, an pancreatitis. The major indirect effects include increased acute and chroni graft rejection, secondary bacterial or fungal infection, development o Epstein-Barr virus–associated posttransplant lymphoproliferative disease accelerated atherosclerosis, and decreased patient and graft survival ***(Madri and Boucher 2008).***

منسّق:لون الخط: أسود

Other indirect effects that may be caused by CMV infection ar Guillain-Barré syndrome and diabetes mellitus. With respect to Guillain Barré syndrome, studies in experimental models suggest that this entity has a immunological basis and that infectious agents such as CMV an *Campylobacter jejuni* are responsible for initiating the immune response tha causes neural damage ***(Pérez-Solaa ~~et al.,~~ et al., 2008).***

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Diabetes mellitus is a common complication in SOT recipients, with a incidence ranging from 3% to 45%. Although the most important cause o post-transplant diabetes mellitus is the effect of immunosuppressive drugs o glycemia control, CMV infection has also been identified as a risk factor fo this entity ***(Pérez-Solaa ~~et al.,~~ et al., 2008).***

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In addition to short-term effects such as acute rejection, CMV diseas has been associated with the two most common causes of late kidney graf

loss: cardiovascular disease and chronic graft rejection ***(Lopez-Rocafort and Brennan, 2001).***

Cardiovascular disease is currently the leading cause of death in a transplant patient with a functioning kidney graft. CMV infection was shown to be an independent risk factor for death from a cardiovascular cause in these patients, especially those with high viral replication ***(Kalil ~~et al.,~~ et al., 2003).***

منسّق:لون الخط: أسود

Similarly, activation of the arteriosclerosis process in small renal arterioles has been associated with the development of chronic allograft nephropathy, which may be explained by the fact that intimal thickening is more intense in CMV-infected patients than in non-infected patients ***(Helantera ~~et al.,~~ et al., 2003).***

منسّق:لون الخط: أسود

With the development of CMV-specific antiviral therapy strategies the incidence of CMV disease has decreased dramatically among solid organ transplant (SOT) recipients, and the indirect effects of CMV disease have been minimized ***(Fishman ~~et al.,~~ et al., 2007).***

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Pre-emptive and prophylactic therapies are used with the goal of avoiding the need for "standard therapy", in which treatment is initiated after clinical signs and symptoms are present. In pre-emptive therapy CMV viremia is monitored and treatment is initiated when CMV viremia reaches a specified threshold, most frequently before the patient becomes symptomatic. Prophylaxis is offered to patients during the period of highest risk of infection to prevent development of CMV viremia and disease. Although debate continues as to which strategy is optimal, there is consensus that both approaches are superior to waiting for symptomatic infection ***(Snydman, 2008).***

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New challenges have arisen with the broad use of antiviral therapy for CMV disease. These include the potential development of ganciclovir resistance, uncertainty about optimal duration of prophylaxis, and the occurrence of late-onset CMV disease. Maribavir, a benzimidazole riboside, is a novel agent in a new class that works by inhibiting CMV DNA synthesis and nuclear export. The development of a safe and effective vaccine that could prevent CMV disease in pregnant women and that could prevent infection and disease in immunocompromised individuals, especially transplant recipients, is a critical need. Many attempts have been made, but they have met little success ***(Madriz and Boucher, 2008).***

منسّق:متوسط، المسافة البادئة: السطر الأول: 0 سم، مسافة قبل: 0 نقطة، التحكم بالأسطر الناقصة/الوحيدة، عدم منع أرقام الأسطر، ضبط المسافة بين النص اللاتيني والآسيوي، ضبط المسافة بين النص والأرقام الآسيوية

منسّق:الخط: (افتراضي) Bold cinnatirB، ٢٦ نقطة، دون غامق، دون مائل، خط اللغة العربية وغيرها: Palatino-Bold، ٢٨ نقطة، دون غامق، (العربية وغيرها) العربية (مصر)، أحرف استهلالية صغيرة

منسّق:تباعد الأسطر: تام 42 نقطة

منسّق:الخط: دون غامق، خط اللغة العربية وغيرها: دون غامق، مائل

AIM OF THE WORK

To study the effect of infection with cytomegalovirus on kidney transplant recipients and the effect on graft outcome, moreover to establish risk factors for infection with CMV in the study population.

منسّق: المسافة البادئة: قبل: 0 سم، السطر الأول: 0 سم

CYTOMEGALOVIRUS

منسّق:لون الخط: أسود

Cytomegalovirus (CMV) was first isolated from the salivary glanc and kidney of two dying infants with cytomegalic inclusion bodies anc reported in 1956. Two other laboratories isolated CMV at approximately the same time. Thus, CMV was initially called "salivary gland virus" o "salivary gland inclusion disease virus". In ***1960, Weller ~~et al~~et al.,*** proposed the use of the term *cytomegalovirus*. Klemola and Kaarianinei first described CMV mononucleosis, the principal presentation o previously healthy individuals, in 1965. CMV was first isolated in a rena transplant recipient in 1965 ***(Brennan, 2001).***

منسّق:الخط: غامق، مائل، لون الخط: أسود، خط اللغة العربية وغيرها: غامق، مائل

منسّق:الخط: غامق، لون الخط: أسود، خط اللغة العربية وغيرها: غامق

منسّق:الخط: غامق، لون الخط: أسود، خط اللغة العربية وغيرها: غامق

منسّق:لون الخط: أسود

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Epidemiology and Virology

منسّق:لون الخط: أسود، مكثف بمقدار 3.0 نقطة

Human cytomegalovirus (HCMV) is a member of the Beta herpesvirinae sub-family of Herpesviridae. It is a widespread pathogen tha infects a majority of the world's population by early adulthood. In fact, by th age of 40, between 50 and 85% of adults are infected by HCMV ***(Selinsky ~~e~~ ~~al.,~~ et al., 2005).***

منسّق:لون الخط: أسود، مكثف بمقدار 3.0 نقطة

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There are eight known human herpes viruses. The HHV arc divided further into three subfamilies: the alpha-herpesvirinae, the beta herpesvirinae, and the gamma-herpesvirinae. The alpha-herpesvirinac include human simplex viruses (HSV) 1 and 2 and varicella zoster virus The beta-herpesvirinae include CMV, HHV-6, and HHV-7. The gamma herpesvirinae include Epstein-Barr virus (EBV) and HHV-8 ***(Brennar 2001).***

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Modes of Transmission

HCMV can be transmitted via saliva, sexual contact, placenta transfer, breastfeeding, blood transfusion, solid-organ transplantatio

(SOT), or hematopoietic stem cell transplantation (SCT). The seroprevalence of HCMV in the human population ranges between 30% and 90% in developed countries, with seroprevalence increasing with age ***(Brennan, 2001)***.

Structure

HCMV is the largest, with a genome of 235 kb encoding 165 genes. The virion consists of a double-stranded linear DNA core in an icosahedral nucleocapsid, enveloped by a proteinaceous matrix (the tegument). Mature virions range in diameter from 200 to 300 nm nanometer. These components are enclosed in a lipid bilayer envelope that contains a number of viral glycoprotein ***(Crough and Khanna 2009).***

CMV is a labile virus and readily inactivated by lipid solvents pH below 5, heat (37°C for 1 h or 56°C for 30 min), and ultraviolet light for 5 min. It can survive on surfaces for several hours. CMV can be stored at 4°C for a few days without loss of infectivity. Storage at -70°C without loss of infectivity is possible for several months. CMV can be stored at 190°C (liquid nitrogen) indefinitely ***(Brennan, 2001).***

The tegument in HCMV is located between the outer lipid membrane and the icosahedral protein capsid, which contains the viral genomic double-stranded DNA. The tegument is generally thought to be unstructured and amorphous in nature although some structuring is seen with the binding of tegument proteins to the protein capsid. The tegument proteins comprise more than half of the total proteins found within infectious virions. Tegument proteins are phosphorylated, but the significance of this and other post-translational modifications to these proteins remains largely unexplored ***(Tomtishen, 2012).***

A common sequence to direct proteins into the tegument has no been identified through either experimental or bioinformatic approaches The process of assembling the viral tegument upon viral egress and disassembly upon viral entry into cells is largely unknown ***(Kalejta 2008).***

Pp65 is the most abundant tegument protein and the majo constituent of extracellular virus particles. However, pp65 is not essentia for the production of new infectious virus particles as evidenced in strains that lack the pp65 gene which can still replicate in culture. Pp65 is the major tegument protein responsible for modulating/ evading the host cel immune response during HCMV infections. pp65's role in immune evasion is largely attributable to its targeting of both humoral and cellula immunity as well as serving as the dominant target antigen of cytotoxic T lymphocytes ***(Tomtishen, 2012).***

It has been demonstrated that pp65 not only prevents immediate early proteins from being recognized by components of the immune system, but it also inhibits the synthesis of the various components involved in the host cell's immune response ***(Odeberg et al., et al., 2003).***

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The kinase activity of pp65 has also been implicated in causing the degradation of the alpha chain in the major histocompatibility class II cel surface receptor, HLA-DR, via an accumulation of HLA class I molecules in the lysosome ***(Odeberg et al., et al., 2003).***

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The glycoprotein , determine the strain of CMV, are used fo cellular entry of the virus, and are the targets of virus-neutralizing antibody. Virus particles are made and assembled in the nucleus and attain an envelope by budding through the inner nuclear membrane. From there, the particles go through the trans-Golgi network, where the virus

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particle becomes pathogenic through proteolytic cleavage of a consensus furin site to form glycoprotein B (gB) ***(Brennan, 2001).***

When HCMV virions fuse with the membrane of host cells, some tegument proteins remain in the cytoplasm, while others migrate to the nucleus of the cell. Other tegument proteins will remain tightly associated to the nucleocapsids, and mediate their delivery to the nuclear pore complex via the microtubule assembly. Several tegument proteins though will have a specific localization within the cell depending on the stage of the lytic cycle ***(Kaletja, 2008).***

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Glycoprotein B (gb) is the CMV UL55 gene product and the predominant human CMV envelope glycoprotein. Because defective virus particles are noninfectious, this process of virion formation may be amenable to development of potential vaccines ***(Jean et al., et al., 2000).***

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CMV replication produces immediate-early (*ie*), early, and late CMV antigens. IE antigens appear in the nucleus of CMV-infected cells 1 to 3 hour after infection and remain present even in latent infection *ie* antigen gene products direct production of both viral and cellular genes. Early antigens appear in the cytoplasm or membrane approximately 3 h after infection. Early antigen gene products direct viral DNA synthesis ***(Brennan, 2001).***

Late antigens appear in the nucleus and cytoplasm within 6 to 24 h after infection. Late antigen gene products direct production of structural nucleocapsid proteins. Immediate early and early antigens are virus induced nonstructural proteins and appear before DNA synthesis. This is important because the mechanism of action of ganciclovir, foscarnet, and cidofovir (the three most common agents used for treatment of CMV) is through interruption of DNA synthesis. Late antigens are virally encoded

structural proteins and appear after DNA synthesis, so their appearance is sensitive to the common antiviral agents. Because of this, monitoring late antigen levels may be more relevant than monitoring immediate early o early antigen levels when assessing response to therapy ***(Brennan, 2001)***.

Immediate-early genes in HCMV can be silenced in certain cel types upon infection though, which results in a latent infection. A laten infection is characterized by the minimization of viral gene expressio and the inhibition of the assembly and egress of new viral progeny. Late infections can reactivate into a lytic infection upon certain environmenta cues, which causes disease and allows viral spread ***(Mocarski ~~et al.,~~ et al. 2007).***

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Reactivation of latent CMV most likely happens through activatio of viral immediate-early (*ie*) gene transcription. Expression of the CMV *ie*-1 and *ie*-2 gene products, which are transcriptional regulatory proteins is necessary for all subsequent phases of the virus replication cycle Because these genes are not transcriptionally active in latently infecte cells, induction of *i.e.* gene expression through activation of the major *i* promoter/ enhancer (MIEP) appears to be required for CMV reactivation Tumor necrosis factor (TNF) mediated activation of nuclear factor-E (NF-B), which subsequently stimulates expression of the MIEP, has a important role and is induced by the allogeneic response afte transplantation ***(De Keyzer ~~et al.,~~ et al., 2011).***

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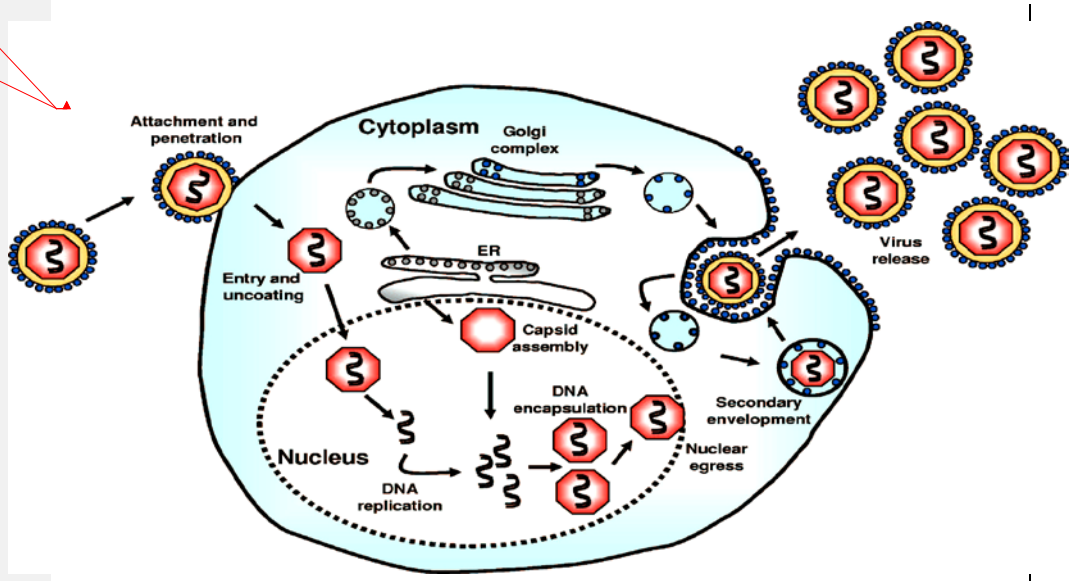

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Figure (1): Life cycle of HCMV in a human cell. HCMV enters human cells eithe through direct fusion or through the endocytic pathway ~~,~~ ***(Crough and Khanna 2009)***.

Immune Responses to Human Cytomegalovirus

Innate Immunity

منسّق:لون الخط: أسود

The innate immune system plays an important role in the ~~defense~~defence against HCMV and also in priming the adaptive immune response. It is becoming increasingly apparent that HCMV is subject to innate sensing by Toll-like receptors (TLRs). The stimulation of TLRs by pathogens such as HCMV activates signal transduction pathways, which induce the secretion of inflammatory cytokines that recruit cells of the innate immune system, and the up-regulation of co-stimulatory molecules such as CD80 and CD86, which are important for the activation of adaptive immunity.

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Natural killer cells play a critical role in control of primary and recurrent CMV infection, typically increasing in response to viral replication ***(Stern ~~et al.,~~ et al., 2008).***

Adaptive Immunity

Humoral responses

منسّق:تباعد الأسطر: تام 12 نقطة

The establishment of long-lasting immunity in response to a primary HCMV infection, which serves to control subsequent HCMV reactivation in the host, is vitally important for preventing uncontrolled replication and serious HCMV disease. HCMV is a potent immunogen that triggers strong immune responses from all arms of the immune system. While the contribution of antibodies for protection against and control of HCMV has been debated, evidence does support a role for humoral immunity in the effective immune response against HCMV and MCMV, predominantly in restricting viral dissemination and in limiting the severity of the disease ***(Boppana and Britt, 1995).***

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Initially, activation of B-cell--mediated immune response leads to the production of immunoglobulin M (IgM), IgG, and IgA antibodies. However, because the virus replicates intracellularly, these antibodies do not offer protection against CMV. It is the cellular immune response mediated by CMV-specific CD4 and CD8 lymphocytes that controls virus replication and provokes long-term protection from CMV disease. However, CMV has certain immunomodulatory properties and influences the production of various cytokines and chemokines that can inhibit natural killer and T-cell responses, as well as target humoral immune responses ***(De Keyzer ~~et al.,~~ et al., 2011).***

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The major target for neutralizing antibodies to HCMV is gB, which is involved in cell attachment and penetration. It is responsible for at least 50% of the neutralizing antibodies in HCMV-infected individuals. gH, which is involved in the fusion of the viral envelope with the host cell membrane, is another target that induces potent virus neutralizing antibodies ***(Crough and Khanna, 2009).***

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There is emerging evidence that a significant number of post transplan patients develop hypogammaglobulinemia (26%–70% in some series) although a link with CMV risk is controversial. Hypogammaglobulinemia was a risk factor for CMV infection in heart and lung transplant recipients bu not in a large cohort of patients post liver transplant ***(Doron et al., et al. 2006).***

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T-cell-mediated immune responses

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The cell-mediated immune response is the predominant mechanism by which HCMV replication is controlled, as with the exception o congenital infection, severe HCMV disease occurs almost exclusively in patients with profound cellular immunodeficiency. While the immune response induced by primary infection does not eradicate the virus, it is clear that HCMV-specific $CD8^+$ T cells & $CD4^+$ T cells are all importan for controlling and restricting viral replication in hosts with persisten infection ***(Crough and Khanna, 2009).***

The CMV virus has developed a number of mechanisms to subver host defenses. One of these is the ability to downregulate expression o major histocompatibility complex (MHC) class I molecules, which may allow evasion of and recognition by cytotoxic T lymphocytes. Human CMV proteins also block transporter associated with antigen processing retain MHC class I molecules in the endoplasmic reticulum, and recycle nascent class I heavy chains back to the cytosol. Because MHC class molecules, acting through various receptors, signal inhibitory messages to natural killer (NK) cells ***(Brennan, 2001).***

T-cell reactivity has been shown to be directed toward a wide range of CMV antigens such as pp65, pp50, IE-1, gB, and others. The key role of T cells in the control of CMV has been demonstrated through the use

of adoptive immunotherapy for both prophylaxis and therapy of CMV infection, primarily in the hematopoeitic stem-cell transplantation (HSCT) setting. For immunotherapy, donor T cells are stimulated in vitro using viral lysate or CMV-specific peptides and then transfused into the patient, resulting in control of CMV replication in most cases ***(Einsele et al., et al., 2002).***

Monocytes are suggested to ~~harbor~~harbour latent cytomegalovirus (CMV) in peripheral blood, which concurs with the finding that all CMV susceptible cells carry the CD13 surface molecule. Data suggest that CMV replicates exclusively in CD13-positive PBMCs ***(Larsson ~~et al.,~~ et al., 1998).***

Natural History

Primary HCMV infection in the immunocompetent host is usually asymptomatic and rarely causes illness. In some cases, it can result in a mononucleosis syndrome, which is clinically indistinguishable from primary Epstein-Barr virus (EBV) infection, with fever, myalgia, lymphadenopathy and hepatomegaly. Tonsillopharyngitis, lymphadenopathy, and splenomegaly are less common symptoms of HCMV infection compared to EBV infection. Other rare complications of primary HCMV infections include arthralgia and arthritis, ulcerative colitis, pneumonitis, hepatitis, aseptic meningitis, and myocarditis ***(Gandhi and Khanna, 2004).***

The virus establishes a life-long infection with some cell being latently infected, a state where the virus has the ability to lie dormant within a cell, while others are persistently infected, where the infection cannot be cleared from an organism and there is intermittent shedding of infectious virions ***(Tomtishen, 2012).***