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CYTOMEGALOVIRUS INFECTIONS IN CHILDREN WITH PRIMARY AND SECONDARY IMMUNE DEFICIENCIES

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Abstract
Cytomegalovirus (CMV) is a human herpes virus that causes significant morbidity and mortality in immunosuppressed children. CMV primary infection causes a clinically mild disease in healthy children, usually in early childhood; the virus then utilises several mechanisms to establish host latency, which allows for periodic reactivation, particularly when the host is immunocompromised. It is this reactivation that is responsible for the significant morbidity and mortality in immunocompromised children. We review CMV infection in the primary immunodeficient host, including early identification of these infants by newborn screening to allow for CMV infection prevention strategies. Furthermore, clinical CMV is discussed in the context of children treated with secondary immunodeficiency, particularly paediatric cancer patients and children undergoing haematopoietic stem cell transplant (HSCT). Treatments for CMV are highlighted and include CMV immunotherapy.

Keywords: child, cytomegalovirus, haematopoietic stem cell transplant

Introduction

Human cytomegalovirus (CMV) or human herpes virus-5 is a member of the Betaherpesvirinae subfamily of the family Herpesviridae [1]. It is a double-stranded DNA virus that causes primary infection, usually in childhood; it is not cleared from the host and becomes latent in white blood cells. In immunocompetent children, primary CMV infection commonly causes a mild illness and is associated with lymphopenia, lymphadenopathy, fever and hepatosplenomegaly. In contrast, CMV has significant implications for children who are or become immunodeficient. This includes those with a primary immune disorder or a secondary immune disorder, acquired due to medical treatment such as immunosuppressive therapy, haemopoietic bone marrow transplant (HSCT) or solid organ transplant [2].

In this review, we discuss the clinical significance and standard and novel treatments of CMV in the primary immunodeficient host, those receiving immunosuppressive therapies for cancer and post-allogeneic HSCT.

Clinical CMV

CMV is a double-stranded DNA virus comprising approximately 235,500 base pairs encoding approximately 165 open reading frames. The genome comprises two unique regions, unique long and unique short, flanked by repeated sequences [3,4,5]. Following the initial infection, CMV is not cleared from the host and establishes lifelong latent infection in undifferentiated $CD34^+$ stem cells and $CD33^+$ myeloid progenitor cells and the $CD14^+$ monocytes and dendritic cells that they mature into

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[6,7]. CMV is also latent in other tissues, such as lung [8]. How CMV is able to establish this lifelong latency is not entirely clear but involves a variety of mechanisms allowing it to evade the host innate immune response [9,10,11]. CMV has evolved sophisticated strategies to circumvent immune cell recognition, encoding arsenals of immunomodulatory molecules—termed immunoevasins—that seek to subvert T cell and natural killer function, allowing it to establish lifelong infections [12].

Restriction enzyme analysis of the CMV DNA demonstrate many genetic variants or strains; however, the differing strains do not allow for classification into distinct genotypes. Furthermore, the corresponding antigenic differences do not define differing serotypes. An individual who has been infected with one strain of CMV does not necessarily have protection from other CMV strains [13,14].

CMV infection can be life-threatening in immunocompromised patients. The broad cellular tropism of CMV results in a diverse range of pathologies and disease manifestations associated with infection. The infection can be a primary infection, a re-infection with a different strain of CMV or reactivation of the virus from latency. The immunosuppressed patients at risk are those with primary T cell immunodeficiency, HIV/AIDS patients, solid organ transplant patients and those undergoing chemotherapy for haematological malignancies with or without the additional immunosuppression, from syngeneic and allogeneic haemopoietic cell transplant as well as the foetus, leading to congenital CMV and neonates with perinatal CMV [2].

CMV in the Primary Immunodeficient Host

Although CMV infection in healthy children and adults is usually mild or asymptomatic, immunocompromised individuals are at risk of more severe disease. Primary immunodeficiencies are a diverse group of disorders that affect 5.6 people per 100,000 in Australia. The most common primary immunodeficiency is antibody deficiency syndrome, which affects 77% of patients [15].

CMV can be transmitted to the neonate by several routes, including transplacentally, through maternal genital secretions during delivery and postnatally via maternal oral secretions, breast milk, objects contaminated with body fluids (e.g., utensils such as drink bottles, dummies/soothers) and via blood products. Local CMV reactivation occurs in the mammary glands at the beginning of lactation, and CMV DNA can be detected in the breast milk of 96% of CMV IgG positive mothers [16,17].

Neonates who are born at term and immunocompetent do not usually have significant CMV disease due to the presence of maternal antibody [18] but may develop mild neuro-developmental sequelae, most commonly neuro-sensory hearing loss. However, the premature neonate, very low birthweight neonate and the neonate with primary immunodeficiency are at a significant risk of severe CMV infection, including pneumonia, hepatitis, neutropenia, thrombocytopenia and enterocolitis [19,20]. Impaired innate and adaptive immune responses contribute to the disease severity [21].

Strategies to reduce the risk of transmission include withholding of breastfeeding whilst maternal CMV status is determined, with cessation if positive, use of CMV negative and irradiated blood products infused with a leucocyte filter and avoiding close contact with young children.

As seen in AIDS due to HIV infection, individuals with T cell dysfunction in the setting of combined immunodeficiencies are also at risk of severe CMV infection. These immunodeficiencies can present in

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infants, older children and young adults with a range of features, including Omenn's syndrome, autoimmunity, granulomas, as well as predisposition to infections. In these individuals, persistent CMV can also drive progression to lymphoid malignancy [21]. A regularly updated comprehensive list of recognised immunodeficiencies is published by the International Union of Immunological Societies (IUIS) [22].

At the other end of the age spectrum, inherited immune deficiency in adults can be responsible for rare cases of significant CMV disease, as demonstrated by an isolated case of fatal disseminated CMV infection in a previously well 51-year-old adult with autosomal recessive NOS2 deficiency [21].

Antiviral Pharmacotherapy

Ganciclovir

The most frequently used drug for CMV disease in the immunocompromised population, including children, is intravenous ganciclovir (GCV), a synthetic nucleoside guanine analogue. GCV is given intravenously as it has very poor oral bioavailability. The main site of action of GCV is the DNA polymerase, UL54. Ganciclovir is a prodrug that must first be phosphorylated for activity. The initial mono-phosphorylation is mediated by the CMV UL97 encoded kinase, resulting in ganciclovir's selectivity for infected rather than uninfected cells [16]. This is followed by further phosphorylation mediated by cellular kinases to a tri-phosphate form.

Ganciclovir has significant cellular toxicity, the main adverse events being neutropenia, anaemia, thrombocytopenia, diarrhoea and fever. The ganciclovir-induced blood dyscrasias are of the most concern in patients undergoing haemopoietic stem cell therapy with neutropenia, increasing the risk of bacterial and fungal infection. Ganciclovir is used for the treatment of sight-threatening CMV disease in AIDS and other severely immunocompromised patients and confirmed CMV pneumonitis in bone marrow transplant patients. Prophylaxis of CMV in solid organ transplant and marrow transplant patients with ganciclovir can be given, generally for defined periods, usually not more than 100 days to limit drug-induced neutropenia and nephrotoxicity. However, CMV disease may still occur after this period as antiviral drugs block viral replication but do not eradicate the virus and, additionally, ganciclovir has no action against latent CMV. Neutropenia is often dose-limiting, often early in therapy, and can be reversed by ganciclovir discontinuation. The ganciclovir-induced neutropenia can preclude the daily use of ganciclovir for CMV prophylaxis after haemopoietic stem cell transplant. In these patients, the CMV viraemia or viral load is monitored with pre-emptive therapy if the viral load exceeds a pre-defined threshold.

Toxicity may be enhanced when ganciclovir is co-administered with other myelosuppressive or nephrotoxic medications. There are animal studies showing that ganciclovir can reduce fertility and spermatogenesis. Safety in pregnancy has not been established as ganciclovir may have mutagenic and teratogenic potential.

Valganciclovir

Valganciclovir is a prodrug of ganciclovir, which, unlike ganciclovir, is well absorbed from the gastrointestinal tract in children and rapidly metabolised to ganciclovir in the intestinal wall and liver.

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The absolute bioavailability of ganciclovir from valganciclovir is approximately 60%. The toxicity and resistance mutations of valganciclovir are the same as ganciclovir. The main advantage of this agent is the ability to dose valganciclovir orally, with better absorption if administered with food.

CMV Immunoglobulin

Human CMV immunoglobulin can be used for CMV infection prophylaxis following bone marrow or renal transplantation and as an adjunct for the treatment of CMV infections such as pneumonitis. It may be of use in patients with poor tolerance of CMV antiviral drugs due to toxicity or those patients with hypogammaglobulinaemia. The role of CMV immunoglobulin remains unclear; at best, it has a limited role in the prevention or treatment of congenital CMV disease [19,].

Cytomegalovirus Vaccines

The development of an effective CMV vaccine would be a significant advance for the management of patients receiving iatrogenic immune suppression. A CMV vaccine would also decrease the rates of CMV infection during pregnancy and in the perinatal period, thus reducing the morbidity of congenital and perinatal CMV. Any CMV vaccine would need to elicit both a strong anybody and cellular response to induce protective immunity. No effective CMV vaccine has been developed to date. A live-attenuated CMV vaccine, derived from the Towne strain, had minimal protection in renal transplant patients or seronegative women [18,19]. More recently, the development of a CMV subunit vaccine based on pp65, an abundant tegmentum protein, and gB, a glycoprotein expressed on the infected cell surface, resulted in boosted antibody, demonstrating up to 50% protection of mothers for CMV infection and recipient-negative/donor-positive solid organ transplant recipients [20,21]. The success of mRNA vaccines in SARS-CoV-2 has stimulated investment in this technology for other pathogens, including CMV. A multi-mRNA vaccine (mRNA-1647) is undergoing dose finding and immunogenicity trials at the current time.

Conclusions

CMV continues to cause significant morbidity and mortality in children with compromised immune systems. The international screening program using TREC is identifying infants with SCID and other T cell lymphopenic diseases, allowing risk modification to prevent opportunistic infections including CMV [24]. This allows for early curative HSCT, which has been demonstrated have a survival benefit if performed under the age of 3 months [24]. CMV is well documented and reported in the allogeneic HSCT patient population but with the current therapies still being ineffective or with significant side effects, leading to difficult CMV treatment. The data on CMV-directed immunotherapy are promising, with recent reports of randomised clinical trials of CMV-directed immunotherapy.

Given the lack of data on the incidence and treatment of CMV outside HSCT, and with the introduction of new agents including CAR T, this sphere needs urgent further investigation and clarification. It is likely that there are unique groups of susceptible patients receiving CAR T and other immunotherapies that will have significant clinical CMV. For these immunosuppressed children, we advocate the identification of at-risk children and strategies for the prevention of CMV primary

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infection, particularly in infants with severe primary immunodeficiencies. For children with secondary immunodeficiencies, we suggest CMV reactivation monitoring and CMV treatment to prevent CMV disease.

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