EDITORIAL

Human Cytomegalovirus: a neglected public health area of significant relevance to women, the foetus and new born. Time for action!

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Persistent infection with human cytomegalovirus (HCMV) infection is extremely common in many parts of the world. Indeed, in the Pakistani population this is reported to be more than 90%, when measured using HCMV specific IgG antibody.[1-4] HCMV-IgMsero-prevalence was 4.3%, but the rate for both IgM and IgG was also 4.1%, indicating that reactivation of latent HCMV infection or reinfection with a new strain is the major cause of IgM seropositivity rather than primary infection.[1] Mujtaba G et al (2016) report 97.5% and 58.5% IgG seropositivity in pregnant women and neonates respectively.[2] Two additional studies by Rizvi CB et al (2015), and Mahmood R et al (2014) report a prevalence of 96.5% and 97.8%in blood donors.[3,4] Similar findings are reported from studies done in Asian, African, and South American countries, in contrast to the much lower HCMV prevalence in North American and European countries.[5-9] HCMV prevalence is high in low-middle income countries, tending to be 20-30% higher in non-white than in white populations.[6,7]

Primary HCMV infection in healthy individuals is usually asymptomatic, and may present with a mild febrile illness, mimicking infectious mononucleosis.[10] HCMV Infection persists for life in a latent form with periodic reactivation or reinfection by a different strain. Common modes of transmission include saliva, tears, milk, urine, stools, blood and bodily fluids, and organ transplant.[5,10] Congenital HCMV infection (placental transmission) can result from primary or secondary (reactivation or re-infection) maternal infection occurring anytime during pregnancy. Congenital HCMV infection can cause intra-uterine growth retardation; brain maldevelopment syndromes; congenital and progressive hearing loss; thrombocytopenia; vision loss; motor disabilities such as cerebral palsy; liver and spleen disorders including hepato-splenomegaly; and other illnesses.[5,6] Notably, infants acquiring primary maternal HCMV infection display much severe form of HCMV-associated sequelae. The epidemiology of vertical transmission of HCMV infection and related congenital anomalies in Pakistani population is not well studied. hHCMV prevalence in South Asian women was higher HCMV prevalence who were born in South Asia compared to those born in UK.[6]

In the west HCMV infects 2 to 4% of pregnant women for the first time as a primary infection during pregnancy, and it is transmitted to the foetus, resulting in a congenital infection in 40% of these pregnant women.[5,8] However, in Pakistan the number of pregnant women infected during pregnancy is not known, but is most probably much higher.[2] Congenital CMV in low- and middle-income countries and is mostly due to secondary maternal infections; whereas, in western settings with moderate levels of seroprevalence (70% in USA) 25% of congenital CMV are due to primary and 75% due to secondary maternal infections, in countries where seroprevalence is relatively low (50% European countries), primary and secondary infections contribute equally for occurrence of congenital CMV infection.[9]

Individuals with HCMV can be co-infected with other widely distributed herpes viruses like Epstein-Barr, and varicella-zoster.[10] These viral infections have a tendency to persist for a lifetime as latent infections. In order to keep the virus in check the immune system mounts a constant response, impacting its effectiveness against other infections, cancer, auto-immune diseases, and response to vaccinations. Such a phenomenon could be one of the reason as to why in Pakistan some of these conditions (cancer, autoimmune, other) present earlier than in the western populations. Moreover, such immune suppression in elderly population has been reported to reduce life expectancy.[11]

HCMV infected blood transfusion can cause severe illness or death among elderly or persons with low immunity.[3] In fact, allogenic stem cell transplant center in Islamabad reported 88% of its patients over a period of five years were HCMV positive and similar number of donors were also CMV positive.[12] Mortality in post-transplant patients was mainly due to CMV enterocolitis/pneumonia, and lack of anti-viral medicines was also one of the major

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problem.[12] Antiviral drug therapy for HCMV prevention and treatment for transplants and selective cases of hearing loss by congenital HCMV carries a high cost of treatment that could vary from US$25,000 to US$30,000.[8,13,14]

HCMV is a seminal neglected public health area of significant relevance to women and children. It infects large swaths of population in the developing world, however, most people across the globe have never heard of it.[5-9] Health care providers do not counsel mothers about CMV transmission.[15] There is significant lack of knowledge and awareness among health care providers and the general population in Pakistan regarding HCMV, modes of transmission and potential consequences of becoming infected. One group who should be made aware of HCMV are females in the reproductive age group and breast feeding mothers. This group is prone as well as a reservoir for HCMV infection, and a source of transmission to the foetuses and neonates.[5,6,9,15,16] Sero-negative women may acquire infection during pregnancy with significant sequelae for the foetus. There is an urgent need for health care professionals in particular all those engaged in prenatal, antenatal and postpartum care of women in rural, peri-urban and urban areas to be educated about HCMV and its mode of transmission.[9,15,16] This requires a vigorous education campaign by local, provincial and national public health organizations.

It is the authors contention that much can be done now to reduce HCMV infection in women of child bearing age and pregnant women thereby reducing HCMV transmission to the foetus and newborn. How can this be done? In the west an approach aptly called the, "CMV Vaccine" has been proposed by experts. There have been successful attempts to develop a vaccine for HCMV that still needs validation studies.[16,17] The administration of the "CMV Vaccine" contextualized for the Pakistani population will reduce HCMV transmission and infection of the foetus and new born.[8,9,15,16] Further to vaccine development, a randomized trial of immunoglobulin and placebo among pregnant women did not reduce vertical transmission of HCMV infection.[18]

There are implications for areas of prevention to be adopted by parents, health care givers, population in general for diagnosis and management of HCMV infection. Estimates of disabilities due to HCMV infection are lacking from Pakistani and similar type of populations. However, western setting population share advancement in clinical virology in all areas of diagnostics and management of HCMV especially since Acquired Immune Deficiency Syndrome (AIDS) patients and transplant recipients remain at high risk of HCMV infection.[19] Low levels of viral replication in latently infected individuals, maintain viral genomes in mononuclear cells and bone marrow, allow subsequent replication in response to inflammation, and low immune states like pregnancy, chemotherapy, corticosteroid therapy. Hence guidelines are needed for infections in such vulnerable hosts in a developing country setting.

In Pakistani population, major task with health care providers is to recommend hygienic precautions such as appropriate hand washing and wearing gloves during diaper change of children especially when performed by seronegative individuals. Raising awareness by instructing mothers and family members to avoid intimate contact with infants and young children may also aid in reducing horizontal transmission of HCMV infection. Other than contact with children, sexual contact may also transmit HCMV to seronegative women. Blood transfusion is common due to endemic thalassemia trait and alternative strategies need to be investigated to reduce the disabilities, morbidity and mortality in debilitated patients who need blood transfusion. As such, 6.6% of the adult population remain at risk of HCMV infection in Pakistan[1] and it is likely that limited use of sharing edibles, and utensils and other hygienic behaviour were responsible for lack of transmission of HCMV infection. However, this needs to be tested in future research to identify the hygienic behaviours determining reduced risk of HCMV transmission in a country like Pakistan with a very high HCMV prevalence. Low socioeconomic status as a determinant of HCMV infection can only be modified, by stringent implementation of public health strategies including HCMV prevention and vaccination programmes on a national level to remove the increasing transmission in existing cohorts of uninfected population.

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