CYTOMEGALOVIRUS INFECTIONS IN PAEDIATRICS

An Essay

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By

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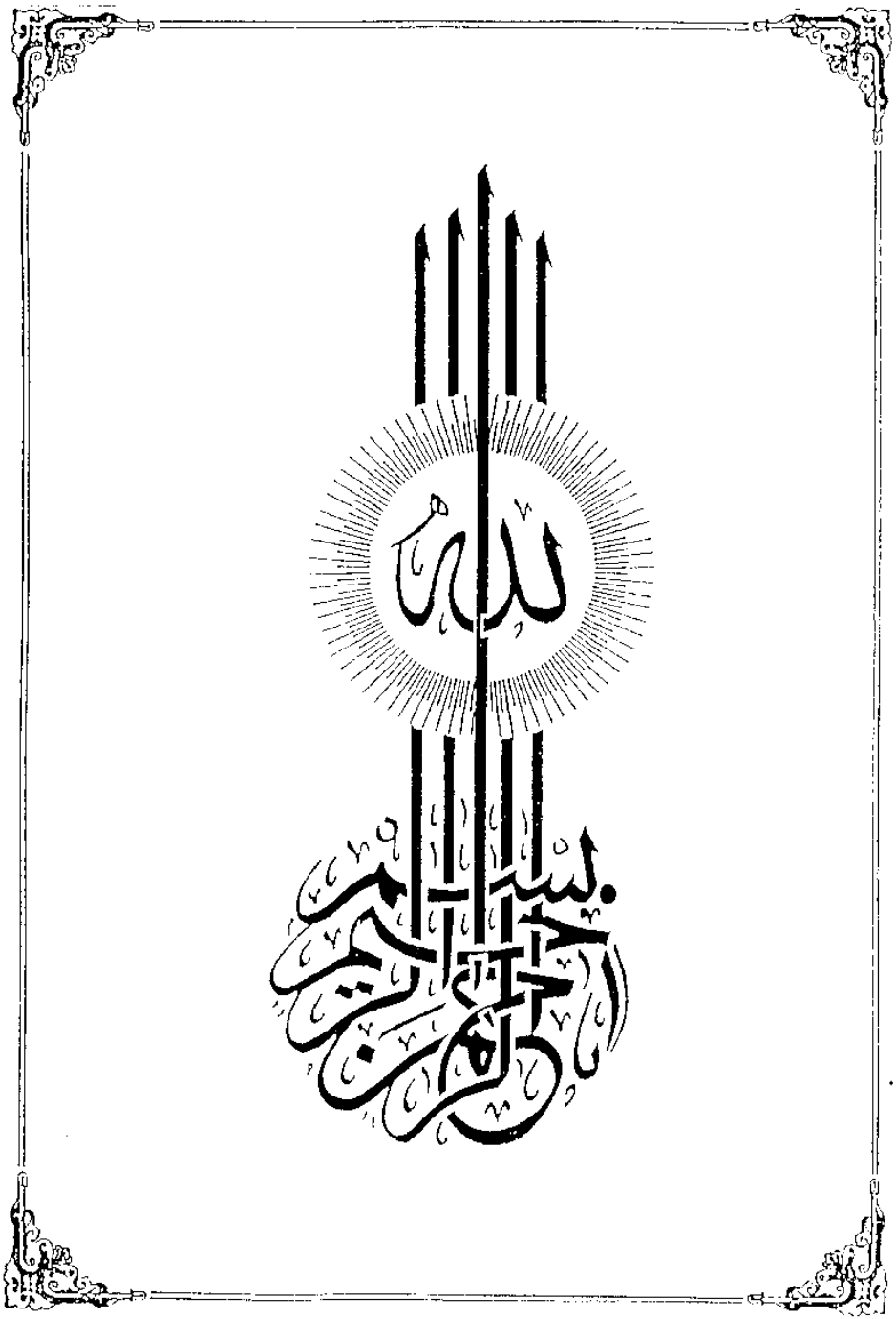

LIST OF ABBREVIATIONS

AIDS: Acquired immune deficiency syndrome.
ATG: Antithymocyte globulin.
BMT: Bone marrow transplant.
CF: Complement fixation.
CID: Cytomegalic inclusion disease.
CMV: Cytomegalovirus.
CNS: Central Nervous System.
DEAFF: Detection of early antigen fluorescent foci.
DHPG: Dihydroxy propoxymethyl guanine.
EBV: Epstein Barr Virus.
ELISA: Enzyme linked immunosorbent assay.
GVHD: Graft-versus-host disease.
HSV: Herpes simplex virus.
HTLV III: Human T-cell lymphotropic virus type 3.
IF: Immunofluorescent antibody.
IFN: Interferon.
IHA: Indirect haemagglutination.
MCMV: Murine cytomegalovirus.
NIEPs: Non-infectious enveloped particles.
RIA: Radioimmunoassay.

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INTRODUCTION

The cytomegalovirus is a DNA virus belonging to the herpes group of viruses. It is the most frequent known cause of congenital viral infections in man. It is endemic throughout the world, occurring in about 0.5% to 2% of all newborn infants. 5-10% of congenitally infected infants may present with hepatosplenomegaly, microcephaly, petechiae, jaundice, chorioretinitis and intracranial calcifications. 90% have no clinical manifestations at birth. About 10% of this population are at a risk for developing a multitude of developmental abnormalities (Stagno et al., 1984).

A far greater number of inapparent CMV infections occurs in neonates as a result of viral transmission from maternal genital tract or breast milk (Kumar et al., 1984). Acquired CMV infection in older children may be asymptomatic or may produce an illness similar to infectious mononucleosis with or without multiorgan involvement (Cohen and Corey, 1985).

The most recent area of CMV morbidity to be appreciated has been its transmission or reactivation in immunocompromised patients especially among organ transplant recipients and AIDS patients. As with other agents whose initial association was detected with only a limited clinical syndrome, CMV has emerged as a ubiquitous virus with host interactions ranging over the full spectrum

health and illness (Krugman and Katz, 1981).

The aim of this essay is to review the subject of cytomegalovirus infections in paediatrics. Our review will include:

* Virology
* Pathology
* Epidemiology
* Clinical features
* Diagnosis
* Differential diagnosis
* Prophylaxis and treatment

HISTORICAL REVIEW

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Late in the nineteenth century pathologists described swollen inclusion-bearing cells in the organs of infants who had died of presumed congenital syphilitic infections. These cells were so large and unusual in appearance that initially they were thought to be amoebae (Ribbert, 1904). Early in 1921 was it suggested by Goodpasture and Talbot that the cellular alterations were not unlike those seen by Lipschütz (1906) in cutaneous lesions of varicella, and they proposed that these large cells were host cells, swollen due to virus-induced injury. A similar view was held by Von Glahn and Pappenheimer (1925) who observed similarities between cytomegalic cells and those seen in herpetic lesions. The investigators were so impressed by the dramatic swelling of these infected cells that they used the term cytomegaly to describe the effect. Later similar inclusion-bearing cells were demonstrated in the salivary glands of some children who had died of a variety of causes. Owing to this propensity to affect the salivary glands, Farber and Wolbach (1932) used the term "salivary gland virus disease". However, since other viruses were known to replicate in salivary glands, Smith et al., (1960) suggested that a preferable description would be cytomegalovirus.

Further progress was delayed until the advent of the tissue culture era. Smith in 1954 was the first to

carry out serial propagation of murine CMV in mouse tissue cultures. Since this success in isolating the virus in tissue culture and the subsequent development of antigens for use in a variety of serological tests, Weller and Hanshaw (1962), and Medearis (1964) have established that human cytomegaloviruses are significant pathogens of the human fetus capable of inducing a wide spectrum of occulo-cerebral defects, as well as a variety of extraneural abnormalities. These observations have been extended and confirmed by numerous investigators in the last decade.

VIROLOGY

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Morphologic Characteristics:

Cytomegalovirus is a member of the herpesvirus family, and is among the largest of viruses, with a diameter of approximately 150 to 200 nm. An inner core consisting of DNA interwined with protein is surrounded by a protein capsid of symmetrical structure composed of 162 capsomeres. This nucleocapsid is covered by a loose amorphous envelope that is derived from the nuclear membrane of the host cell. Loss of this envelope greatly reduces virus infectivity (Pagano and Lemon, 1981) (Fig. 1).

Antigenic Composition:

The relatively large herpesvirus genome contains sufficient genetic information to encode probably more than 50 different proteins, placing CMV among the more complex viruses of man. Many of these proteins, serve as efficient antigens. Despite the identical morphologic appearance of the herpesviruses, human CMV strains are antigenically unrelated to other human herpes viruses. However, they are related to CMV-like agents isolated from non-human primates. As with HSV, strains of CMV demonstrate considerable antigenic diversity when analyzed either by neutralization kinetics or complement fixation. However, no definitive grouping of strains on the basis of antigenic differences has yet emerged (Pagano and Lemon, 1981).

In CMV infected cells, two sets of virus-specific antigens and antibodies appear at different times, as was noted by immunofluorescence techniques. "Early antigens" represent the presence of viral DNA, and appear in the absence of viral replication. After the advent DNA synthesis, so-called "late antigens" appear in the nuclear and cytoplasmic inclusion bodies. Early and late antigens induce corresponding antibodies detectable by indirect immunofluorescence. Other antibodies produced in response to CMV infections are detected by neutralization, CF, and indirect haemagglutination procedures (Ramvani and Hanshaw, 1981).

Viral Multiplication:

Replication of the virus appears to be relatively slow, and newly made infectious particles are first detected at 48-72 hours after infection of cell cultures, with a low virus-to-cell multiplicity. Under these conditions cytochemical and immunofluorescent techniques best reveal the synthesis of viral proteins and the development of the cytologic lesions that accompany viral multiplication, namely, focal lesions, followed by generalized cytopathic changes including rounding of cells and the appearance of large intranuclear oesinophilic inclusion bodies. The first biosynthesis of DNA and accumulation of early and late viral proteins are detected initially in the nucleus. Electron microscopic studies show that viral particles, like herpes simplex virions, are assembled

in the nucleus, attain their envelope at the nuclear membrane, and may form cytoplasmic inclusions or dense bodies. The maturation of viral particles appears to be inefficient; only rare completely assembled virions can be detected among many incomplete particles (many of these are non-infectious dense bodies formed by envelopped viral proteins without DNA or assembled capsids). Hence the yield of infectious virus in cell culture is low, and as many as 10^6 particles are needed to initiate infection of a new culture. Most infectious virus remains cell-associated, and therefore the addition of intact infected cells to a culture initiates viral propagation most efficiently (Dulbecco and Ginsberg, 1980).

Viral replication is dependent on host cell metabolism which can be arrested experimentally by blocking cellular DNA or protein synthesis. Such metabolic inhibitors can induce a state of viral latency. Conceivably, similar requirements to viral replication may be responsible for the phenomenon of persistent or latent infection seen in vivo (Panjvani and Hanshaw, 1981).

Host Range and Susceptible Host Cells:

Many species of animals are infected with their own specific cytomegaloviruses, but no laboratory animal has proved susceptible to infection with cytomegaloviruses of humans. Virus has been isolated and propagated only in cultured human fibroblasts (Dulbecco and Ginsberg, 1980).

In vivo, however, virus appears to multiply in a variety of cell types, including many of epithelial morphology. CMV replicates in the epithelial cells of the respiratory tract, salivary glands, and kidney; in the kidney the tubular cells shed virus for prolonged periods. In addition, CMV is frequently present in cervical secretions, especially late in pregnancy. The virus may also be found in the semen in CMV mononucleosis after its disappearance from other sites; the exact site of replication in the male genital tract is uncertain. As with other herpes viruses, spread via the blood stream is accomplished by cell-associated viraemia, the virus being associated with both lymphocytes and polymorphonuclear leukocytes. Cell susceptibility to human CMV is strikingly affected by age. Infections in utero result in devastating destruction of the central nervous system, whereas encephalitis from post-natal CMV infection is exceedingly rare (Pagano and Lemon, 1981).