CYTOMEGALIC INCLUSION DISEASE

JOHN R. F. GUY*

Halifax, Nova Scotia

Cytomegalovirus infection was believed for sixty years to be caused by an infectious agent. However, the virus causation of cytomegalovirus infection was not established until 1956 when Smith isolated inclusion-producing virus from the salivary gland of a seven month old infant dying of adrenal carcinoma and from renal tissue of a second infant dying of cytomegalic inclusion disease.

Before this, cytomegalic inclusion disease was considered a rare and fatal disease found in infants dying of a syndrome resembling erythroblastosis fetalis, sepis, congenital toxoplasmosis or congenital syphilis. Pathognomonic inclusion-bearing cells were found in the salivary glands and it was assumed that these instances were not clinically significant.

Cytomegalic inclusion disease was rarely found in adults and when it was found. it was found in patients dying of disease producing impaired resistance.

The recent isolation of cytomegaloviruses has provided both the detection of active infection during life and the basis for development of the complement fixation test which can be used diagnostically.

It is being gradually realized that these agents have biological properties in a combination that makes them important and potent pathogens for man.

ETIOLOGY:

As mentioned, Smith isolated cytomegalovirus from two cases in 1956. Weller and associates in the following year isolated identical agents from three living infants with clinical cytomegalic inclusion disease. At the same time, they demonstrated the value of urine isolation in antemortem diagnosis. Rowe and associates (1956) were successful in isolating similar virus in degenerating cultures of adenoid tissue from the three infants.

These isolated viruses had properties which enabled them to be included as members of a single group. Some of these properties were:

1. Agents grew only in fibroblastic cultures of human origin.
2. Progressed slowly with development of focal lesions consisting of groups of enlarged, rounded, highly refractile cells which contained large intranuclear inclusions.
3. Focal lesions slowly increased in number and size over a period of weeks with gradual appearance of the cytopathic effects.
4. More rapid generalized effect followed the inoculation of specimens of high virus titre or after serial propagation and adaptation of the virus to the **in vitro** system.

Prenatally infected infants were found to have neutralizing antibody early in neonatal life even in the presence of persistent infection.

An infant's serum is capable of neutralizing his own cytomegalovirus strain but a variable neutralizing capacity has been noted in cross-neutralization tests using sera from other infected infants. This is less apparent in sera obtained from children with acquired infections.

INCIDENCE:

Seroepidemiologic studies using the complement fixation test have shown that cytomegalovirus infection is a fairly common event. Approximately 50% of women of child bearing age have evidence of previous infection. This antibody is passively transferred to the newborn infant. In young children, antibody is relatively infrequent.

As would be expected, the percentage of seropositive individuals in an area may reflect the living conditions. Stern and Elek in London found 4% of 6 month – 5 year old children were seropositive while in Puerto Rico, Mendez-Cashion found antibody in 20% of children of a similar age group.

In London and Rochester, 15% of 5 – 10 year olds have antibody while Rowe et al found

*Third Year Medicine, Dalhousie University

complement-fixing antibody in 40 – 50% of institutionalized children in the same age group. It is to be noted that these are long term confinements such as found in children institutionalized for tuberculosis. Isolation rates for children in a general paediatric ward were similar to those of well children living at home.

TRANSMISSION:

Virus is present in the urine and saliva, so transmission is primarily through contact with these excretions. Prenatally infected infants acquiring the infection vertically from the mother are prime sources of spread throughout families and institutions. However, the transmission of the infection requires close physical contact.

Patients, especially infants, who are known or suspected to have active cytomegalovirus infection should be considered potentially hazardous to pregnant women.

CLINICAL MANISFESTATIONS OF CYTOMEGALOVIRUS INFECTION:

The clinical spectrum of reported cases to date has probably been distorted somewhat in that the more classical and more severely affected patients have been studied virologically. Infants born after subtle intrauterine encephalitis have development closer to, but significantly different from, that of abnormal children. The preschooler who suffers from behaviorial, speech, hearing and perceptual problems could easily have been exposed to such a gestational influence without overt disease in the mother or significant illness in the neonatal period.

Cytomegalovirus infection in a newborn, including the first year of life, has produced sequelae related to infection of the central nervous system in 81% of cases. These sequelae include such central nervous system defects as microcephaly, paraparesis or diplegia, chorioretinitis and cerebral calcification. These defects lead to definite retardation of mental development in these children.

Enlargement of liver and spleen is variable in degree but is usually present sometime during the observation of virus-positive infants in the first year of life. Other more frequently-observed extraneural manifestations are hepatitis, pneumonitis, papular rashes, obstructive hyperbilirubinemia and hemolytic anemia. In congenital cytomegalovirus infection, one or more of these symptoms are present during the neonatal period and in the majority of these cases the prognosis is grim. Manifestation of these symptoms after this period presents the possibility of an acquired infection.

This is supported by the appearance of both inapparent and clinical disease in patients with leukemia, Hodgkins disease and lymphoma. The patients undergoing immunosuppresive therapy for organ transplantation have been found to carry a high risk of infection and disease.

DIAGNOSIS:

Diagnosis of cytomegalovirus infection in infants presents a challenging problem. There are many diseases that resemble cytomegalovirus infection, and a differential diagnosis is varied. The differential would include "failure to thrive", cerebral palsy, hepatosplenomegaly, jaundice, persistent respiratory infection, thrombocytopenia and a variety of oculocerebral defects.

Infants with cytomegalovirus infection usually show multisystem involvement, but they may present with only a petechial rash with associated splenomegaly. Infants with unexplained "neonatal hepatitis", purpura, microcephaly, chorioretinitis, persistent pneumonitis, optic atrophy, hemolytic anemia or hepatosplenomegaly should be regarded as possible cases of cytomegalovirus infection. Close resemblance to cytomegalovirus infection is imparted by congenital rubella, toxoplasmosis and disseminated herpes-virus infection.

Acquired infection may be suggested by the presence of unexplained hepatosplenomegaly and mildly abnormal liver function tests. Viral pneumonitis or hepatitis in patients with malignant disease or conditions associated with defective antibody synthesis should suggest the possibility of acquired or reactivated cytomegalovirus infection.

Neonatal infection is invariably associated with disease and is always vertically transmitted. In about 50% of such patients, it is possible to demonstrate pathognomonic cells with nuclear inclusions in the urine sediment.

The best method of establishing cytomegalovirus infection at any age is direct isolation of the virus from the urine. The agent may then be propagated in a variety of human fibroblastic cultures. The isolation of cytomegalovirus from the throat or urine establishes infection but does not establish the presence of disease due to these agents, especially in isolations made after infancy.

Generally the younger the viro-positive patient, the more likely he is to have symptoms resulting from his cytomegalovirus infection. There may be difficulty deciding whether the virus is etiologic or incidental in some patients.

The complement fixation test can be used and has been used as a screening test in infants.

Approximately 1% of infants have a titre in contrast to the nearly uniform presence of titre in infected infants. This separation is less valuable with increasing age as infection is acquired during childhood.

Some patients will be poor producers of antibody, a circumstance which predisposes them to cytomegalovirus infection and yet also precludes the use of this serodiagnostic method. For such persons, direct virus isolation and histologic examination are other available means of establishing the presence of infection.

The medical art is not so cut and dried that we cannot find some authority for doing whatever we please. If your doctor does not think it good for you to sleep, to drink wine, or to eat of a particular dish, do not worry; I will find you another who will not agree with him.

Montaigne