PREVALENCE OF CYTOMEGALOVIRUS INFECTION IN EGYPTIAN PATIENTS WITH CHRONIC HEPATITIS C

Thesis

Submitted for fulfillment of Master Degree in Tropical Medicine

BY

Ahmed Mohmed Salah Mohmed Al-Emam
M.B,B.CH,

Supervised By

Prof. Dr. Ahmed Noaman Mohamed Haseeb
Professor of Tropical Medicine
Faculty of Medicine - Ain Shams University

Dr. Amal Tohamy Abed El-Moez
Assistant Professor of Tropical Medicine
Faculty of Medicine - Ain Shams University

Dr. Amal Ahmed Abas
Assistant Professor of Clinical Pathology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain shams University
2012

معدل انتشار عدوى فيروس تضخم الخلايا في مرضى الالتهاب الكبدي الفيروسي(ج) المزمن

رساله

رسالة توطئة للحصول على درجة الماجستير
في الأمراض المتوطنة

مقدمة من

الطبيب/ احمد محمد صلاح محمد الإمام
بكالوريوس الطب والجراحة

تحت إشراف

أ.د/ احمد نعمان محمد حسيب
أستاذ الأمراض المتوطنة
كلية الطب - جامعة عين شمس

د/ آمال تهامي عبد المعز
استاذ مساعد الأمراض المتوطنة
كلية الطب - جامعة عين شمس

د/ أمـــل أحمـــد عبـــاس
استاذ مساعد التحاليل الطبية
كلية الطب - جامعة عين شمس

كليـــة الطـــب
جامعة عين شمس
٢٠١٢

SUMMARY

This study included fifty patients with chronic hepatitis C related cirrhosis and fourty three healthy controls. Full history taking and complete clinical examination were done for every case. As regards laboratory part of the work the following laboratory investigations were carried out: complete blood count (CBC), liver profile (serum albumin, serum bilirubin, ALT, AST and Alkaline phosphatase), HBs Ag and HCV Ab and blood sugar (FBS, 2hr pp). Also abdominal Ultrasono-graphy was done. The immunological part of the work was the estimation of the antibody titre for cytomegalovirus both (IgG) and (IgM) by ELISA.

The results of clinical examination revealed hepatomegally in 41 cases (82%), splenomegally in 46 cases (92%), ascitis in 46 cases (92%), lower limb oedema in 29 cases (58%), haematemesis in 5 cases (10%), fever in 21 cases (42%) and there is no case had lymph node enlargement.

Estimation of antibody for cytomegalovirus IgM was negative in 34 cases (68%) and positive in 16 cases of CMV IgM (32%). As regard of CMV IgG titre was negative in 17 cases (34%) and positive in 33 cases (66%).

There was a higher mean CMV IgM among cases 1.42 compared to 0.4 among controls and the difference is highly significant statisatically.

List of Contents

List of Tables

List of Figures

List of Abbreviations

Ab	Antibody
ADE.....	Antibody dependent enhancement
AIDS.....	Acquired ImmunoDeficiency Syndrome
ALT	Alanin transferase
APCs.....	Antigen presenting cells
AST.....	Aspartate transaminase
CBC	Complete blood count
CMV	Cytomegalovirus
CTL.....	Cytotoxic T lymphocyte
D^+/R^-	Donor positive/ Recipient negative
DHF	Dengue haemorhagic fever
DNA.....	Deoxyribonucleic acid
E/M	Electron microscopy
EBNA1	EBV-encoded nuclear antigen-1
EBV	Ebstein Barr Virus
eIF2α.....	eukaryotic initiation factor 2 alpha
ELISA.....	Enzyme-inked immunosorbant assay
FBS	Fating blood sugar
gm	gram
HBs AG	Hepatitis B surface antigen
HBV.....	Hepatitis B Virus
HCMV	Human Cytomegalovirus
HCV.....	Hepatitis C virus
HDV.....	Hepatitis D Virus
HHV.....	Human herpes virus
HIV	Human Immunodeficiency Virus
HLA.....	Human leukocyte antigens
HSV	Herpes simplex virus
HTLV	Human T-cell Leukaemia-lymphoma Virus
Ig.....	Immunoglobulin
IL	Interleukin

List of Abbreviations (Cont...)

INF-γ.....	Gama interferon
LA.....	Latex agglutination
MHC	Major Histocompatibility Complex
mm	millimeter
mRNA.....	messenger Ribonucleic acid
neg	negative
NK	Natural killer
PCR.....	Polymerase chain reaction
PD	Programmed cell death
PKR	Protein kinase R
PP.....	Phosphoprotein
RBC	Red blood cell
RNA.....	Ribonucleic acid
SD	Stadared deviation
Th.....	Help T lymphocyte
VVI	Virus-virus interactions
WBC	white blood cell
µm.....	micrometer
$2^{/}$-$5^{/}$OAS	$2^{/}$-$5^{/}$ Oligoadenylate synthetase
2hr pp.....	two hour postprandial

INTRODUCTION

Infection with Cytomegalovirus (C.M.V) is found throughout all geographic locations and socioeconomic groups ***(Griffiths and Walter, 2005).*** C.M.V. infection can also be life threating for patients who are immuno compromised e.g. patients with HIV, organ transplant recipients, or neonates ***(Vancikovà and Dvoràk, 2001).*** Infectious C.M.V. may be shed in the body fluids of any infected person, and can be found in urine, saliva, blood, tears, semen, and breast milk ***(Schleiss, 2006).*** In patients with depressed immune system, C.M.V. related disease may be much more aggressive ***(Barry et al., 2004).*** C.M.V. hepatitis may cause fulminant liver failure. Because of the frequency of C.M.V. with AIDS up to 100%, some authors thought that C.M.V. to be the etiologic agent. A lot of work has been done on depressed cell mediated immunity in endemic hepatosplenomegaly ***(Fledmier et al., 1984; Gastle and Feldmeier, 1984),*** hence the incidence of C.M.V. could be increased in patients with chronic liver disease.

AIM OF THE WORK

The aim of this work is to study the prevalence of Cytomegalovirus infection in patients with chronic hepatitis C related cirrhosis.

CYTOMEGALOVIRUS INFECTION

Cytomegaloviruses (CMV) are a group of viruses within the beta herpes virinae subfamily of herpes viridae family. Infection with this group of viruses typically results in a characteristic enlargement of cells with the appearance of distinctive intranuclear and cytoplasmic inclusion bodies which has led to common name of cytomrgalovirus ***(Smiley and Huang, 1990).***

Humans are the only known host of cytomegalovirus. It is endemic in all parts of the world, epidemics are unknown. It is present throughout the year, with no seasonal variation seen in infection rates. The prevalence of infection varies with socioeconomic status, Living conditions and hygienic practices ***(Jawetz et al., 1995).***

New infections are almost always asymptomatic. After infection, virus is shed from multiple sites (urine, saliva, semen, breast milk and cervical secretions). Viral shedding may continue for years, often intermittently, as latent virus becomes reactivated. Thus exposures to CMV are wide spread and common ***(Jawetz et al., 1995).***

Mode of Transmission:

Transmission requires close person to person contact. Virus may be shed in urine, saliva, semen, breast milk and cervical

secretions and is carried in circulating white blood cells. Oral and respiratory spread are probably the dominant routes of cytomegalovirus transmission ***(Jawetz et al., 1995).***

1- Maternofetal transmission:

Maternal infection play an important role in transmission of CMV to neonates, CMV can be reactivated during gestation and the virus may be transmitted to the fetus in utero despite circulating maternal antibody. The transmission occur through transplacental route from infected mother to the fetus, passage through birth canal during labour, from milk by breast feeding as milk is the most commn site of CMV excretion ***(Baynor, 1993).***

2- Sexual transmission:

a) Heterosexual:

Several types of evidence, direct and indirect document heterosexual transmission of CMV. Higher rates of cervical infection are found in woman who are highly sexually active ***(Ho, 1990).***

So it is very likely that both the uterine cervix and semen are important reservoirs of CMV and play a role in disease transmission during heterosexual activity ***(Ho, 1990).***

b) Homosexual transmission:

There is epidemiologic as well as biologic evidence that CMV may be transmitted by homosexual activity. First, that

homosexual practice is associated with acquisition of CMV infection in the male is well documented. Second, homosexual men often have evidence of chronic active infection, this is manifested by frequent presence of CMV in semen and urine and high prevalence of IgM antibody to CMV in homosexual men ***(Smith and Singer, 1992).***

Compared with heterosexual men, homosexual men are significantly more likely to be CMV culture positive. Infection in homosexual men is associated with increased age, number of sexual partners and the practice of anal receptive intercourse ***(Smith and Singer, 1992).***

3- Transfusion transmission:

Primary or recurrent CMV infection occasionally follows blood transfusion and several studies provide conclusive data to indicate that blood transfusion is an important source of CMV infection ***(Galea, 1992).***

Transfusion products that are unlikely to transmit cytomegalovirus infection can be prepared by filtration to remove leukocytes, use of cryopreserved red cells or can be obtained by selecting donors who are seronegative for antibodies to CMV. These products are indicated for certain groups of immuno-suppressed patients including pregnant women who are CMV seronegative, premature infants of low birth weight (less than 1200gm) who are born to CMV seronegative mothers, CMV

seronegative recipients of allogenic bone marrow transplants from CMV seronegative donors and CMV seronegative patients with the acquired immunodeficiency syndrome ***(Sayer et al., 1992).***

4- Organ transplantation transmission:

Transplantation of an organ from a seropositive donor into a seronegative recipient results in primary CMV infection of recipients, with a wide variation of clinical symptoms depending upon the immunosuppressive regimen ***(Smyth et al., 1991).***

Cytomegalovirus pneumonia is a major cause of morbidity and death following lung transplantation. The case fatality rate is highest in the CMV seronegative recipients of organ from seropositive donors, which suggests that transmission of CMV may occur with graft, but in seropositive recipients the comparative importance of reactivation of endogenous virus and reinfection with donor virus is poorly understood ***(Smyth et al., 1991).***

The risk of developing CMV infection post bone marrow transplantation is significant (41% in pairs in which donor and or recipient were CMV seropositive in contrast to 0% in neg/neg donor/recipient pairs).

This risk can be predicted by pretransplant serostatus, diagnosed by monitoring expression of the lower matrix protein pp 65 of CMV on peripheral blood cells and correlates with transplant related morbidity. The latter appears to be reduced by early treatment with ganciclovir ***(Bacigalupo et al., 1992).***

5- Nosocomial transmission:

Nosocomial infections with CMV are an areas of great concern and controversy within the medical community. It is possibly transmitted via workers hands or contaminated fomites. CMV has been recovered from objects used in the care of an infected newborn and from surface in a day care centre up to 8 hours after virus excretion occurred ***(Roman et al., 1991).***

6- Child to parent transmission:

Children are likely source of infection to their non immune mothers who may be pregnant or have subsequent pregnancies. Naturally, this is of concern also to institutions such as day care centers and hospitals. Where women of childbearing age are in frequent contact with young children. Child to parent transmission may be reduced by increasing protective behaviors (handwashing and glove use) and decreasing risky behaviors (intimate contact between child and parent) ***(Finmey et al., 1993).***

7- Child to child transmission:

Grouping of young children for day care also results in more widspreade CMV nfection, so the risk of acquiring CMV appears to be significantly greater for children in day care than for those cared for at home. The recovery of CMV from toys that had been recently mouthed by children known to be excreting the virus suggested that the exchange of infected saliva through fomites could play a role in the spread of CMV in day care centers ***(Adler, 1991).***