A recent highlight on the incidence and prevalence of HBV and HCV in multitransfused children

Thesis

Submitted for partial fulfillment of MD degree in Pediatrics

By Ali Ragheb Ali Al-Ayyat M.B., B.Ch., M.Sc. Pediatrics

Supervisors

Prof. Dr. Normeen Kaddah

Professor of Pediatrics Faculty of medicine, Cairo University

Prof. Dr. Sawsan Abd Alhadi

Professor of Pediatrics Faculty of medicine, Cairo University

Prof. Dr.Azza Mostafa

Professor of Clinical Pathology Faculty of medicine, Cairo University

Ass. Prof. Dr. Ahmad Maher Kaddah

Assistant Professor of Pediatrics Faculty of medicine, Cairo University

> Faculty of medicine Cairo University 2009

Acknowledgment

First and foremost thanks to Allah, the All Beneficent and most Merciful.

Words will never be able to express my deepest appreciation and my profound gratitude and thanks to my **eminent professor Prof. Dr.**Normeen Kaddah, Professor of Pediatrics for her kind supervision, helpful advice, great encouragement and generous cooperation.

I would like to express my endless thanks to my eminent Professor **Prof. Dr. Swsan Abd Alhadi,** Professor of Pediatrics; for her kind continuous support, great encouragement and extremely generous cooperation.

I would like to thank **Prof. Dr. Azza Mostafa**, Professor of Clinical Pathology; for her generous supervision, continuous encouragement, kind advice and sympathy through this work.

I am also deeply grateful to **Prof. Dr. Ahmad Maher Kaddah**, Assistant Professor of Pediatrics for his great efforts, kind patience, continuous encouragement, advice and sympathy.

Especially, I would like to give a very special tribute to my family who gave me love, patience and faithful support.

Abstract

New children Hospital of Cairo University and receiving washed filtered blood regularly. All Candidates were subjected to detailed history taking, thorough clinical examination, and Laboratory evaluation including: complete blood count, liver enzymes, serological tests for HBV(serum HBs Ag and Serum Hepatitis B Core Antibody IgM) and for HCV(Anti-HCV antibody).

Key word:

Incidence

Prevalence

HBV HCV

List of abbreviations

Abbreviation	Original Word
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Antibody to hepatitis B core antigen
Anti-HBs	Antibody to HBV surface antigen
APTT	Activated partial thromboplastin time
CJD	Creutzfeldt - Jakob disease
CMV	Cytomegalovirus
DDAVP	1-deamino-8-D-arginine vasopressin
DIC	Disseminated intravascular coagulation
EBV	Epstein - Barr virus
ECMO	Extracorporeal membrane oxygenation
EFS	Event-free survival
EIA	Enzyme immunoassay
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FNHTR	Febrile nonhemolytic transfusion reactions
GBV-C	GB virus C
GVHD	Graft versus host disease
HAI	Histologic Activity Index
HAV	Hepatitis A virus
HBcAg	Hepatitis B core antigen

HBeAg	Hepatitis B e antigen
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B virus DNA
Hct	Hematocrite
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E
Hgb	Hemoglobin
HGV	Hepatitis G virus
HHV-4	Human herpesvirus 4
HHV-5	Human herpesvirus 5
HHV-6	Human Herpesvirus 6
HHV-8	Human Herpesvirus 8
HIV	Human Immunodeficiency Virus
HIV NAT	HIV nucleic acid amplification testing
HLA	Human leucocyte antigen
HPV-B19	Human parvovirus B19
HTLV-I/II	Human T-Lymphotropic Viruses type I and II
IFN-alpha	Interferon alfa
MALT	Mucosa-associated lymphoid tissue lymphoma
MU/m²	Million units per square meter
NAT	Nucleic acid testing
NHL	Non-Hodgkin's lymphoma

PCR	Polymerase chain reaction
PT	Prothrombin time
RBCs	Red blood cells
RDP	Random donor platelets
REAL	Revised European American Lymphoma
RIA	Radioimmunoassay
RMSF	Rocky Mountain Spotted Fever
SDP	Single donor platelets
SEN-V	SEN virus
SVR	Sustained virological response rate
TA-GVHD	Transfusion-associated graft-versus-host disease
TRALI	Transfusion-associated acute lung injury
TSEs	Transmissible spongiform encephalopathies
TTM	Transfusion transmitted malaria
TTP	Thrombotic thrombocytopenic purpura
TTV	TT virus
WBCs	White blood cells

C	Contents	
•	List of Abbreviations	I
•	List of Tables	IV
•	List of Figures	\mathbf{V}
•	Introduction and Aim of the Work	VIII
•	Review of literature	
	Blood transfusion in pediatrics	1
	Transfusion transmitted diseases	15
	Hepatitis B virus	26
	Hepatitis C virus	54
•	Patients and methods	••••
	81	
•	Results	86
•	Discussion	100
•	Summary	115
•	Conclusions	118
•	Recommendations	119
•	References	120

List of tables VII

List of Tables

Table	Subject	Page
(1)	Guidelines for transfusion of RBCs in patients < 4 months of age	3
(2)	Guidelines for transfusion of RBCs in patients > 4 months of age	4
(3)	Correlation between HBV serotypes and genotypes.	29
(4)	Epidemiology and modes of transmission of hepatitis B virus infection	30
(5)	Serologic markers for the different phases of acute and chronic hepatitis B virus infection	40
(6)	Interpretation of the Hepatitis B Panel	41
(7)	Medical terms of hepatitis	43
(8)	Descriptive statistics of patients with frequent blood transfusion included in the study	86
(9)	Frequency of demographic data of patients with frequent blood transfusion included in the study.	87
(10)	Anthropometric evaluation	88
(11)	Age distribution of cases	88
(12)	Sex distribution of cases	89

List of tables VIII

(13)Residence of cases 89 Comparison anthropometric between 90 (14)measurements of patients with frequent blood transfusion included in the study in relation to HCV transfusion included in the study in relation to HCV Comparison between demographic, 91 (15)anthropometric and laboratory data of patients with frequent blood transfusion included in the study in relation to HCV..... Clinical evaluation of liver and spleen in (16)92 relation to duration of transfusion in sickle cell anemia (group 2)..... Clinical evaluation of liver and spleen in 93 (17)relation duration of transfusion to thalassemics (group 1)..... Descriptive statistics of demographic (18)94 laboratory data of thalassemic patients (group 1) in relation to duration of transfusion Descriptive statistics of demographic and 95 (19)laboratory data sickle cell anemia patients (group 2) in relation to duration transfusion..... Prevalence of HCV in multitransfused patients, (20)96 thalassemics (group 1) and sickle cell anemic (group 2) patients Prevalence of HCV in multitransfused patients (21) 96 in relation to duration of transfusion

List of tables IX

Prevalence HCV multitransfused in (22) 97 thalassemics (group 1) in relation to duration of transfusion. Prevalence of HCV in multitransfused sickle 97 (23)cell anemia patients (group 2) in relation to duration of transfusion..... Comparison between HCV status before and (24) 98 after introduction of antibody testing in thalassemic patients..... Comparison between HCV status before (25) 98 after introduction of antibody testing in sickle cell anemia patients.....

List of figures VII

List of figures

Figure	Subject	Page
(1)	Map of HBV genotype distribution	28
(2)	Serology of acute and chronic HBV	42
(3)	Window period of acute HB	44
(4)	The HCV genome and expressed polyprotein	55

Introduction:

Hepatitis B and hepatitis C virus infections are considered to be important health problems worldwide (Peksen, 2004).

More than 400 million people are chronically infected with hepatitis B virus (HBV) all over the world. At least 20-30% of them will die of complications of chronic liver disease including liver cirrhosis and cancer. This led the world health organization (WHO) to place HBV in the top 10 causes of death worldwide (Gish and Locarnini, 2004).

In pediatric patients, HBV accounts for 10-20% cases of acute hepatitis and remains the most important cause of chronic hepatitis (Singh and Pradhan, 2003).

WHO estimated that more than 227 million individuals have been infected with hepatitis C virus (HCV) and more than 170 million are carriers of HCV all over the world. Of persons with chronic hepatitis C, 10-20% will develop cirrhosis and 1-5% will develop hepatocellular carcinoma (El-Kamary et al., 2003).

The prevalence of HCV antibodies is reported to be higher in Egypt than any other country (**Arthur et al., 1997**). Studies of the epidemiology of HCV infections have suggested that the Nile Delta region of Egypt has among the highest prevalence rates of HCV in the world with seroprevalence rates of 30-40% in those over the age of 30-yrs (**Darwish et al., 2001**).

Rational background:

HBV can be spread by transfusion of infected blood or coagulation factor concentrates. In the 1960, the risk of transfusion-associated HBV was 50% and Hepatitis B surface antigen (HBsAg) was detected in up to 60% of patients with post transfusion hepatitis (Anderson and Ness 2000).

Although the exclusion of paid donors and the application of HBV serological screening dramatically reduced incidence of HBV infection to the extent that only 80 cases of transfusion-associated HBV infection are reported in the United States annually, post-transfusion HBV continues to be the most common cause of hepatitis B due to the fact that screening of donor blood units for HBsAg does not exclude all blood units infectious for HBV (Pereira,2003).

Hepatitis C virus accounts for more than 90% of post transfusion chronic hepatitis and cirrhosis (Wiley et al., 2002). In fact, blood transfusion remains an important past and a potential current risk for HCV transmission in developing countries, where anti–HCV screening is limited by technical and financial factor (Lesi and Kehind, 2003).

Repeated blood and blood product transfusions in many pediatric diseases such as beta-thalassemia major, sickle cell anemia, hemolytic anemia, hemophilia and aplastic anemia, is necessary for patient survival. However, they will increase exposure to HBV and HCV infections (Al-Shayyab et al., 2001).

Objective:

The aim of this study is to evaluate the annual incidence of HBV and HCV in diseased Egyptian children who received blood transfusion with special stress for new cases who received blood in less than 1 year. Variety of patients are receiving blood or blood product transfusion especially new cases attending hematology clinic of pediatric hospital of Cairo university in the last six months and coming one year. They include hemolytic anemia cases (thalassemia, sickle cell anemia), aplastic anemia and hemophilia. Work will be done for one year duration.

All patients will be subjected to:

- Thorough history taking for their diagnosis and history of exposure to blood or blood products in detail.
- History of vaccination to HBV.
- Thorough clinical examination.
- Liver function tests.
- Screening for hepatitis HBsAg and screening for antibody to hepatitis B core antigen (IgM).
- Screening for hepatitis C antibody by enzyme-linked immunoassay III.
- Statistical analysis: Essential statistical analysis will be arranged.

Hypothesis:

In most countries, blood donations are routinely screened for HBsAg as well as for HCV, human immune deficiency virus (HIV) and syphilis (Mollah et al., 2003).

In Egypt, screening for HCV is based on detection of antibodies to recombinant antigens which include antigens from structural and non-structural regions. Second generation assay for HCV was used in Kasr Al-Aini hospital blood bank in the early 1990. Third generation assay (ETI-AB-HCVK-3) was first used in Kasr Al-Aini hospital blood-bank in 1998 and is still used till this moment.

In the early 1976, HBsAg detected by hemeagglutination was used in Kasr Al-Aini hospital blood-bank hospital .Further; HBsAg detected by enzyme immuno assay (ET1-MAK-4) was first used in Kasr Al-Aini hospital blood-bank in 1980 and is still used till now.

Although screening for HCV and HBV has reduced the risk of infections from transfusion of blood and blood products, new infections continue to occur either due to donor infections that escape detection or by inefficient decontamination of products during preparation (Irshad and Peter, 2002).

Accurate estimates of the risk of transfusion of HBV and HBC infections are essential for monitoring the safety of the blood supply and evaluating the potential effect of new screening tests. The most direct way of estimating the risk associated with transfusion is to study the rate of infection prospectively in transfusion recipients (**Arora et al., 2003**).