REVIEW ON HEPATITIS D VIRUS INFECTION
(DELTA AGENT)

ESSAY

Submitted for partial fullfilment

for the Master Degree in

Tropical Medicine

By

DEVY NASSEEM GAID

M.B.B.Ch (Assuit University)

Supervisors:

Prof. Dr. ABD EL-RAHMAN EL-Ziady

Professor of Tropical medicine

AIN SHAMS UNIVERSITY

Dr. MOHAMED FAWZY MONTASER

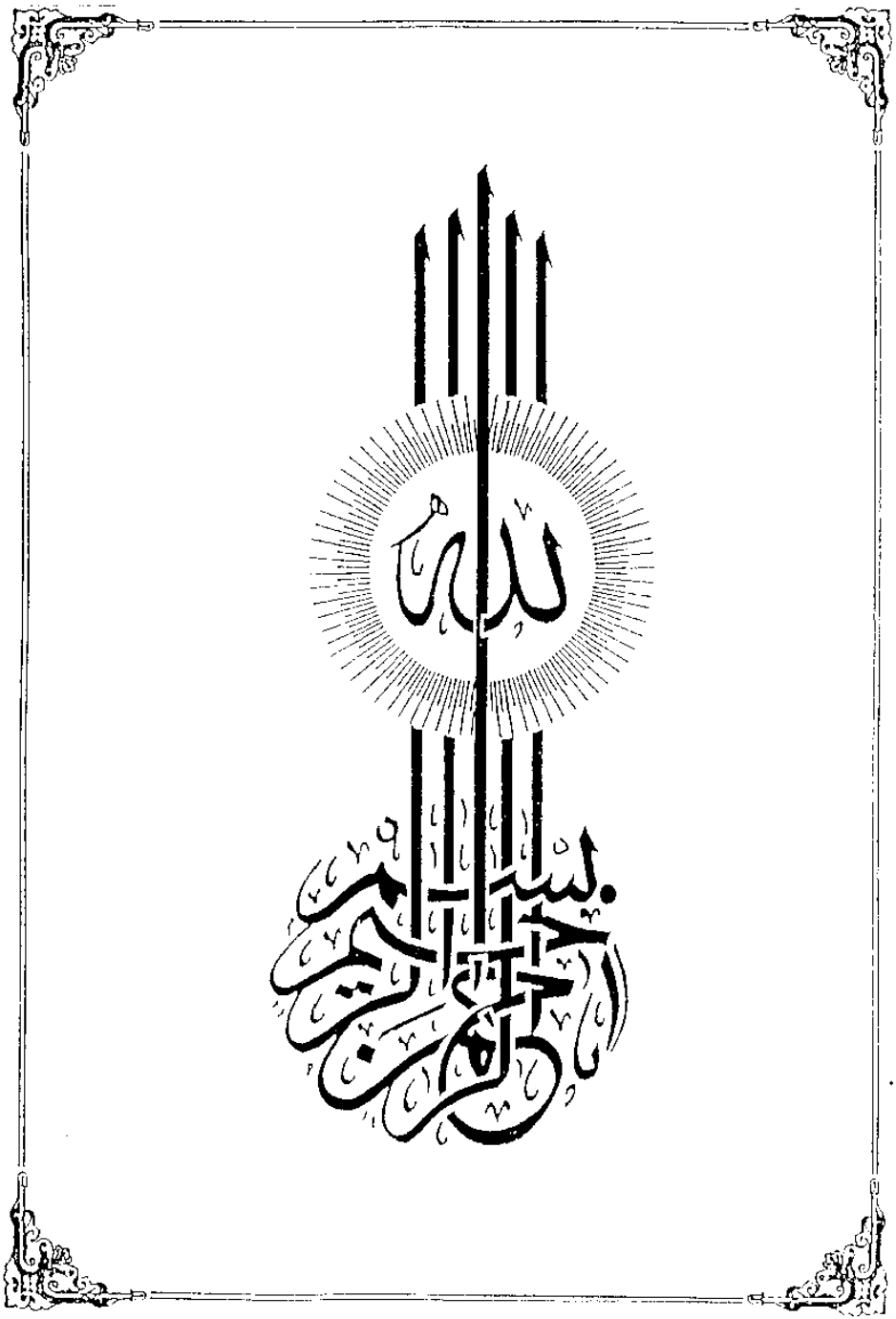
Lecturer of Tropical Medicine

AIN SHAMS UNIVERSITY

Faculty of Medicine
Ain Shams University
1986

CONTENTS

1111111111



ACKNOWLEDGEMENT

This essay has been performed in the department of endemic diseases and Tropical medicine, Ain Shams University hospitals , Cairo, Egypt.

I would like to express my deepest gratitude and cardial thanks to Prof. Dr. El-Ziady, Professor of Tropical Medicine, Faculty of Medicine, Ain Shams University . Who has been generous with his Knowledge, experience, advice and continuous supervision throughout the whole work.

Thanks and gratefulness to Dr. Mohamed Fawzy Montaser Lecturer of Tropical Medicine , Faculty of Medicine. Ain-Shams University for his generous helping , supervision and kind guidance given throughout the course of this work . I would like to express my thanks to all members of tropical Medicine department for their assistance .

******

INTRODUCTION

INTRODUCTION

The term δ Ag was first introduced in 1977 to designate a new antigen observed in the hepatocyte nuclei of Italian HB_sAg carriers with chronic liver disease ; δ Ag was considered to be an antigenic varient of HB_cAg. Subsequent epidemiologic data and transmission experiments in chimpanzees, however, established that δ Ag was a marker of an infectious agent , the delta agent (δ). As documented in the subsequent studies , there were a coniderable body of data to indicate that δ , although dependent on HBV for its expression and replication , represents a unique hepatitis agent , distinct from HBV. This conclusion was based on the following evidence :

1) The lack of cross-reaction between δ Ag/anti- δ and HBV--specific Ag/Ab systems; .
2) The lack of hamology between the δ -associated RNA and HBV DNA based on hybridization analysses ;
3) Terminal dilution experiments in chimpanzees in which the dilution endpoint of δ in a serum far exceeds that of HBV and ;
4) The successful transmission of δ of human origin to WHV carrier Woodchucks indicating that other HBV-Like viruses can provide the requisite helper functions for δ infection.

Important observations based on clinical , epidemiologic and histopathological features of patients with acute

REVIEW OF LITERATURE

AETIOLOGY

Structue and Physico-chemical Characters of Delta Virus:

In 1977 Rizzetto et al., discribed a new antigen that was detected by immuofluorescence in the nuclei of hepatocytes from Italian patients with chronic type B Hepatitis.

The antigen resembled hepatitis B core antigen , Untile discripant results revealed it to be antigenically distinct from HB_cAg , but related in some way to chronic infection with HB virus .

The antigen was never found in biopsies from patients with HB_sAg negative hepatitis and only a proportion with HB_s Ag Positive hepatitis had the antigen or the antibody to it (Arico et al. , 1978) . In subsequent studies carried out in United States, Rizzetto was able to extract delta antigen from the liver of fatal case of hepatitis. Within the liver , the delta antigen is localized to hepatocyte nuclei with guanidine hydrochloride yields a protein with a molecular weight 68,000 and buoyand dene-sity in Cscl of 1.28g/cm^3 (Rizzetto et al., 1980b).

Physiochemical and enzymatic treatment of the antigen reveals no loss of activity following heat , 2m M NaEDTA ,detergents (0.5 % Na deoxycholate, Nonidet P-40,

or Tween 80) ether , 1% DNase I or RNase A , glycosidase or acid (30 min. at ph 2.4) . Conversely , partial or complete loss of antigenic activity has been observed after treatment with Alkali (Ph 10.6) ,5 M Na thiocyanate , 3 to 6 M guanidine Hcl, I .% trichloroacetic , and proteolytic enzymes (0.1 % trypsin , Chemotrypsin or pronase) . (Rizzetto et al. , 1980b).

In the blood , the delta agent is surrounded by a HB_s Ag envelop , it has a particular size 35 - 37 nm and buoyant density in Cscl of 1.24 to 1.25 g/cm^3 (Rizzetto et al., 1980c). **Fig. 1.**

No capsid has been observed , and only one serotype has been recognized . Being surrounded by HB_s Ag , it is precipitated by anti-HB_s. The genome of delta agent consists of a 1.75 Kilobase RNA with a molocular weight of $5.5 X10^5$ daltons. No homology with HBV genome has been found using hybridization techniques . Disruption of the particles with detergent releases delta antigen and RNA genome .

In 1983a Rizzetto et al., designated the delta agent as hepatitis D virus or delta virus.

Animal Susceptibility

Infectivity studies have shown that chimpanzees are susceptible to delta infection (Rizzetto et al., 1980a). The inocula contained both hepatitis B virus and delta agent in animals without previous markers of hepatitis B produces a self-limiting acute hepatitis with markers of both hepatitis B virus and delta infection , the incubation period being 3-4 weeks when highly infectious material was used and 12 - 13 week with less infectious material. In chronic HB_s Ag carrying chimpanzees acute self limiting hepatitis was seen.

The HB_s Ag titre was temporarily lowered before delta antibodies developed. Thus Transmission of delta to HB_sAg carrier chimpanzees results in inhibition of synthesis of HBV gene products (HB_s Ag and HB_cAg) but acute hepatitis coincident with the intrahepatic expression of delta (Rizzetto et al., 1980a).

Experimental transmission of delta agent to the Eastern Woodchuck (Marmota Monax) was proved by Ponzetto et al. , 1983a where 3 chronic WHV carriers were inoculated with the delta agent . All had circulating woodchuck

hepatitis surface antigen (WH_s Ag) . evidence of delta infection was found in all three woodchucks and the course was simular to that described in chimpanzees (Rizzetto et al., 1980a). Inoculation of serum from the first passage to another chronic WHV carrier resulted in higher levels of delta antigen in serum, at least twice as much as that produced on first passage. Woodchuck delta antigen was circulating within a capsid provided by WHV . There was marked inhibition of synthesis of the marker of WHV seen coincidence with appearance of delta Ag in serum. Typically . WH_s Ag levels decreased while delta Ag was rising , and they remained temporarly depressed thereafter . WHV-DNA in serum fell to an almost undetectable levels as soon as delta-Ag appeared, But quickly returned to pre delta values once δ -Ag was cleared from the blood .

Since WHV can provide"helper" effect to delta agent , it is possible that other HBV-like viruses are able to do so .

EPIDEMIOLOGY

Epidemiology

Introduction to Epidemiology

Hepatitis D virus formerly called the delta agent (Rizzetto et al., 1983a). is an RNA virus whose genome and inner protein are encapsulated by a coat consisting of HB_sAg (Rizzetto et al., 1980b , Bonine et al., 1981) .

It is a defective virus depending on hepatitis B virus infection for its replication and expression and capable of infecting only HB_s Ag positive individuals.

Human HB_s Ag carriers expressing delta in the liver mostly develop anti-delta Antibody in the blood . Since development of Anti delta is related to intra hepatic production of delta (Rizzetto et al., 1977) , the serological detection of this anti delta by radio-immunoassay provides a tool for recognizing delta infection and studying its epidemiology (Rizzetto et al., 1979) .

Geographical Distribution & Mode of Transmission :

Through studies of the prevalence of IgG and IgM antidelta antibodies (Rizzetto et al., 1980b) . (Smedile et al., 1982a) , seroepidemiological surveys have shown that delta infection is wide spread but that its distribution around the world is not uniform.