
DISCOVERY OF HEPATITIS E VIRUS - THE UNTOLD STORY

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COMMENT

Viral hepatitis is a cause of considerable morbidity and mortality, both from acute and the chronic sequelae. It is a global health problem and breaks all known human barriers in causing disease and suffering. Globally over 850 million are chronic carriers of hepatitis B and C and account for over 2 million deaths per year. However, epidemics of jaundice had been a menace to humanity since antiquity. The first description of viral hepatitis is attributed to Hippocrates (460-375 BC), who described the clinical features of epidemics of jaundice have been feature of many military campaigns and have been determining factor for defeat and victory of historical wars. Epidemic jaundice was thought to be catarrhal in origin. This concept was forwarded by Bamberger (1855) and supported by Virchow (1865). It was postulated that the initial lesion was gastroduodenitis followed by spread of catarrh to the epithelium of the bile ducts, thereby producing an obstructive jaundice. This concept was defeated by studies of Dible (1943), who performed needle biopsies of the liver on patients with epidemic jaundice and proposed hepatocellular damage or "hepatitis" as the underlying cause of epidemic jaundice. The most important human experiments in the history of viral hepatitis were that of Krugman et al who distinguished infectious hepatitis from serum hepatitis by the use of transmission studies at the Willowbrook State School in New York, an institution for the mentally retarded, where viral hepatitis was an epidemic disease. This was a conclusive study which could not be repeated today. Blumberg et al (1965) made a breakthrough study when he published his classic paper on Australia antigen. This subsequently led to the discovery of hepatitis B virus. Feinstone et al (1973) visualized hepatitis A virus particles by immune electron microscopy in stool extracts of patients with acute HAV virus infection was quickly controlled. Two groups (Alter et al & Tabor et al) of investigators reported that 90% of post-transfusion hepatitis were of not related HAV & HBV. These were the first indication of an existence of another human hepatitis virus. These two papers gave the concept of non-A, non-B hepatitis. It took a number of years before Choo et al identified hepatitis C virus from post-transfusion non-A, non-B hepatitis and developed serological test for its diagnosis. Hepatitis C virus is of major importance globally in causing chronic hepatitis, cirrhosis and hepato-cellular carcinoma. While all these major discoveries of hepatitis viruses were occurring, the status of epidemic jaundice which had introduced the subject of hepatitis to humanity remained ignored. A number of epidemiological shifts had occurred to the epidemic jaundice over the 100 years since it had been described. Epidemics had limited to regions of the developing world with low socio-economic status, bad sanitation and unsafe water supplies. Epidemics of jaundice in Indian subcontinent were reported on regular intervals, involved hundreds and thousands of people with considerable morbidity and mortality. In fact epidemic jaundice was a national health problem in India. An epidemic of jaundice which hit Delhi, the capital of India, in 1955-56 caused estimated

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JK-Practitioner2004;11(3):291-294

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29,300 of jaundice. This epidemic was studied by Indian Council of Medical Research and reported as a classical hepatitis A disease. However, diagnostic tests for hepatitis A virus were not available and done on these sera to confirm or refute the diagnosis.

During this period, I was a DM trainee in Gastroenterology and Hepatology at Postgraduate Institute of Medical Education and Research, Chandigarh, India from June 1976 to June 1978. During this period I was most impressed by some aspects of viral hepatitis in North India. Repeated epidemics of viral hepatitis were reported from number of regions, with high morbidity and mortality. Fulminant hepatitis was seen in high percentage in third trimester pregnant women with high maternal and fetal mortality. Viral hepatitis in pregnant women in the West was not reported to have high incidence or severity. Data from the developing countries were seen with skepticism as bias could not be ruled out from hospital reported data. In fact till that time no well reported field epidemiological study on epidemic hepatitis had been done. Professor D.V. Datta with whom I was most impressed as a researcher during my DM training would call to the Liver laboratory for a cup of strong coffee following the morning meeting and ask me in his typical Punjabi style "Sultan, why do women come with fulminant hepatitis and die." He knew I did not know the answer but yet was eager to find out my response. With these thoughts about viral hepatitis and pregnancy in India deeply engrained in my mind, I returned to Kashmir to practice Gastroenterology as a consultant in Internal Medicine at the Government Medical College Srinagar, Kashmir, India. In November, 1978, a large scale epidemic of jaundice was reported in over 200 villages in District Baramulla of Kashmir valley. A major panic was announced due to magnitude of disease involving young adults and deaths in pregnant women. An opportunity had come for me to define the data clinical duties and responsibilities, visited the epidemic affected area in the next 2 days, and approached the health services for manpower support to do a door to door survey for new cases of jaundice. We were in the field for house to house study within two weeks of the first report of the epidemic. Sixteen affected villages with a population of over 16,000 were identified as the study area. Over the next 6 months each house was visited weekly and all members were examined for possible symptoms and signs of hepatitis. Blood samples were examined for possible and randomly selected non-affected persons

for biochemical and virologic studies. A research laboratory was established in the Medical College Campus to receive process and store sera. International support was sort to test sera for hepatitis A and hepatitis B virus infections. Originally 35 sera were tested in Birmingham for HAV and HBV infection. Subsequently a large pool of sera was tested in Netherlands, Japan and USA. Following these preliminary sera analysis, support from Netherlands in the form of kits was received and we performed hepatitis A and hepatitis B in our Medical College laboratory. Concurrent with the field study, Medical College hospital was used to further study admitted patients for clinical presentation and liver histology by performing percutaneous needle biopsies of nonfulminant cases and postmortem biopsies of fatal fulminant cases. Results of epidemiological data, virologic studies and histological findings were available in May 1979. Critical analysis of data were remarkable in the conclusions. The data were convincing that (i) the epidemic curve was highly compressed lasting for less than 6 weeks and was of common source type, (ii) the disease was caused by a hepatitis virus, (iii) the agent was spread through contaminated water, (iv) the agent was of non-A, non-B type, (v) epidemic involved young adults with sparing of children (vi) there was high incidence and severity of disease in pregnant women and (vii) liver histology in a subgroup of patients revealed characteristic histological findings. In fact the disease incidence and severity in latter pregnancy was so remarkable that we had difficulty in finding a third trimester pregnant women at the tail of the epidemic disease. We estimated that the epidemic had involved 200 villages with a population of over 600,000 and had caused icteric disease in 20,000 individuals with 600 deaths. These data were reported to national and international societies and published in American Journal of Medicine in 2 original articles. The first article (Khuroo MS: Study of an Epidemic of Non-A, Non-B Hepatitis: possibility of another human hepatitis virus distinct from post-transfusion non-A, non-B type. *Am J Med.* 1980;68:818-24) postulated the existence of another human hepatitis virus of non-A, non-B type which was enterically-transmitted, water-borne and distinct from post transfusion non-A, non-B type (latter identified as hepatitis C virus). The second article (Khuroo MS, Teli MR, Skidmore S, Sofi MA, Khuroo MI: Incidence and Severity of Viral Hepatitis in Pregnancy. *American Journal of Medicine* 1981;70:252-5) was exclusively dedicated to incidence and severity

of disease in pregnant women as depicted from house to house field study. The data showed that this disease has extremely high mortality in third trimester of pregnancy. This article for the first time confirmed earlier observations of high prevalence and mortality of viral hepatitis in pregnancy so impressively seen in the hospital rounds in India.

The description of this epidemic led to subsequent transmission (Balayan et al *Intervirology* 1983; 20:23-31) and clonning (Reyes et al *Science* 190; 247:1335-9) of Hepatitis E virus. In fact, 13 years later, analysis of the sera collected during this epidemic revealed HEV to be cause of the epidemic (Skidmore et al *J Med. Virology* 1992;37:58-66). The original paper has been reproduced in the book "Classic Papers in Viral Hepatitis" edited by Christine A. Lee and Howard C. Thomas, Science Press, 1988, page 184-190. On discovery of hepatitis viruses, Robert H. Purcell from NIH Bethesda MD wrote "Simultaneously with these studies, Mohammad Sultan Khuroo, another young gastroenterologist, was studying water borne epidemic of hepatitis in the mountainous Kashmir region of North India. The hepatitis in Kashmir... Thus the fifth recognized human hepatitis was discovered and initially called epidemic or enteric ally transmitted NANB hepatitis virus and subsequently designated HEV." (Purcell H. The discovery of hepatitis viruses. *Gastroenterology* 1993; 104:955-63).

Kashmir was hit by a series of large scale epidemic over the next decade and the epidemiology of these epidemics was similar to that reported from the index epidemics. Overall 52,000 icteric cases of viral hepatitis were recorded from these epidemic, with over 2000 deaths. A number of studies were performed during these epidemic to unraval the enigmatic epidemiology of epidemic hepatitis E and these studies have found place in respectable journals. A number of studies were performed on sporadic hepatitis and fulminant hepatitis in Kashmir and major role of HEV in the etiology of these 2 entities was highlighted.

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