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FULMINANT LABREA HEPATITIS - THE ROLE OF HEPATITIS A (HAV), B (HBV), C (HCV), AND D (HDV) INFECTION. (PRELIMINARY REPORT)

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An unusual type of fulminant hepatitis, known as Labrea Hepatitis (Labrea Black Fever), has been documented in the Brazilian part of the Amazon Basin [1, 2, 8, 9, 10, 12, 13]. Described for over 50 years[10], this disease is characterized by severe hepatitis (rapid course) resulting in hepatic failure and death [2, 12, 13]. Children, adolescent and young adults are mainly affected [1, 12]. The availability of histopathological liver specimens from cases of Labrea Hepatitis, showing a specific picture of microvesicular steatosis (morula-like cells) and eosinophilic necrosis, has been pointed out by Brazilian authors[9]. This pattern are different from those of massive and submassive necroses found in ordinary fulminant viral hepatitis. Similar clinical and histologic features of Labrea Hepatitis were found in northern Colombia[5], western Venezuela[16] and Central African Republic[17].

Recent studies suggest that hepatitis Delta virus (HDV) infection of hepatitis B virus (HBV) carriers is responsible for the etiopathogenesis of Labrea Hepatitis[2, 13]. Several studies have recently characterized the Amazon basin as a high endemic area for HBV and HDV infection[2, 14, 15].

The purpose of the present study was to confirm the participation of HDV in the etiopathogenesis of Labrea Hepatitis. Serum samples from 11 patients (4 males, 7 females; aged 3 - 38 years; mean age 13.1 years), with post-mortem histopathological diagnosis of Labrea Hepatitis were screened for the presence of hepatitis viral markers: HAV (IgM antibodies to hepatitis A [IgM anti-HAV], Hepanostika, Organon Teknika, B. V. Holland); HBV (hepatitis B surface antigen [HBsAg], IgM antibodies to hepatitis B core antigen [IgM anti-HBc], Sorin Biomedica, Saluggia, Italy); HCV (antibodies to hepatitis C [anti-HCV], Organon Teknika, UBI HCV EIA, N. Y., USA) and HDV (Delta antigen [HDAg], IgM antibodies to hepatitis Delta [IgM anti-HD], Sorin Biomedica, Saluggia, Italy) were submitted to the enzyme immunoassay (EIA).

Serum HBV-DNA (hepatitis B virus deoxyribonucleic acid) and HDV-RNA (hepatitis D virus ribonucleic acid) were assayed using molecular hybridization technique, as previously described[3, 18].

On the basis of serological tests, acute Delta infection was diagnosed in four patients (36.4%). Two of this had acute HBV and HDV infection (HBsAg, IgM anti-HBc, IgM anti-HD) and the other two had chronic HBV infection (without IgM anti-HBc and HBV-DNA) with superimposed acute HDV infection (one case: HBsAg, IgM anti-HD; one case: HBsAg, HDAg, HDV-RNA). Two patients (18.2%) had acute HAV and HBV infection (IgM anti-HAV, HBsAg, IgM anti HBc). Two patients (18.2%) had acute HBV infection alone (HBsAg, IgM anti-HBc). One (9.1%) had acute HAV infection alone (IgM anti-HAV). One (9.1%) had acute HBV and HCV infection (HBsAg, IgM anti-HBc, anti-HCV). Finally, one (9.1%) patient had acute HCV infection alone (Anti-HCV). The time between the first clinical manifestations and death of 11 patients, ranged from 3 to 8 days (mean of 4.6 days).

All specimens showed a diffuse small-droplet fatty change, lytic and eosinophylic necroses with different degrees of intensity, were also seen, without evidence of massive or submassive necrosis. "Morula-like cells" were more frequently found in HDV acute superinfection, as well as in HAV/

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HBV acute coinfection and acute HCV infection, and less often in other forms of viral hepatitis. Lobular architecture was preserved and portal tracts revealed bile duct proliferations, mononuclear inflamatory cells infiltration.

Figure 1 shows the presence of "morula-like" cells in hepatic tissue in the fulminant form of hepatitis A (HAV), B (HBV), C (HCV) and Delta (HDV).

In this series only 4/11 (36.4%) of the patients with Labrea Hepatitis had serological evidence of acute infection by HDV. These results differ from previous studies that demonstrate a great correlation (74.0%) between the infection by HDV and Labrea Hepatitis, suggesting that the "morula-like"

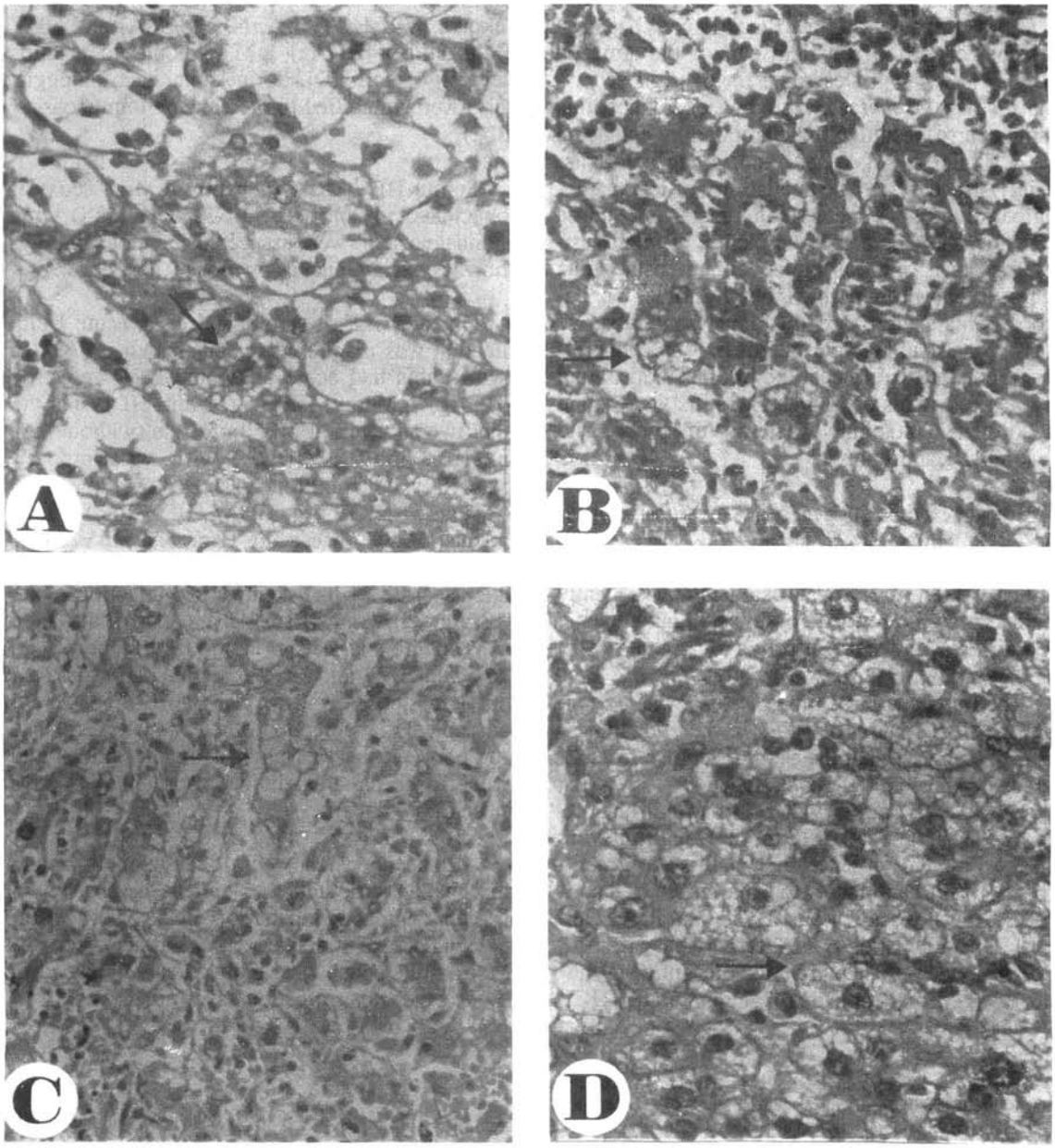

Fig. 1 - A) Fulminant hepatitis type A ("morula - like" cells - arrow), H & E, 200X. B) Fulminant hepatitis type B ("morula - like" cells - arrow), H & E, 250X. C) Fulminant hepatitis type C ("morula - like" cells - arrow), H & E, 200X. D) Fulminant Delta hepatitis (superinfection in HBV carrier - "morula - like" cells - arrow), H & E, 300X.

cells are pathognomonic of HDV superinfection in HBsAg carriers[2].

Our study demonstrate that 63.6% of patients with Labrea Hepatitis had evidence of infection by HAV, HBV and HCV, either alone or simultaneously. These data differ from others authors who consider the infection by HDV the main cause of Labrea Hepatitis[2]. The idea that other hepatitis viruses could be involved in the etiopathogenesis of Labrea Hepatitis, HBV infection alone, lesser contribution of HAV, and Non A - Non B agents, now termed hepatitis C virus[7], was suggested recently[2]. This hypothesis is strengthened in the present study.

The use of sophisticated and specific tests for serum markers of HBV (HBV-DNA), HCV (anti-HCV), and HDV (HDAg, HDV-RNA), permitted in this study the confirmation of the envolviment of other viral agents in the etiology of Labrea Hepatitis.

In additon, the etiopathogeny of Labrea Hepatitis could be related to genetic, immunological or age factors. This hypothesis thus remains controversial and requires further studies. On the other hand, experimental transmission studies shows antigenic variation of HDV in Bangui Hepatitis with the same clinical and histological characteristics of Labrea Hepatitis[11]. In this study the authors suggest a possible role for a variant HDV strain which could be responsible for severe hepatitis in Bangui. Recent data, described a new hepatitis B virus strain[4] and this new HBV variant (pre-core mutation) is responsible for fulminant hepatitis in Greek patients[6].

The hypothesis that variant strains of HAV, HBV, HCV and HDV could determine changes in the immune response of local patients leading to this severe form of hepatitis should be taken in consideration. However only experimental studies and the use of advanced techniques such as RNA and DNA amplification, cloning and sequencing of these viral agents could confirm this hypothesis.

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