Fulminant hepatic failure in children and adolescents in Northern Brazil

Insuficiência hepática fulminante em crianças e adolescentes no Norte do Brasil

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ABSTRACT

The histological findings of fulminant hepatic failure were correlated to the demographic, clinical, biochemical and virological features in children and adolescents, native to the Amazonas State in Northern Brazil. 96.2% had evidence of infection by primary hepatotrophic viruses. Histological analysis revealed three distinct patterns of fulminant hepatic failure.

Key-words: Hepatitis. Fulminant hepatic failure. Epidemiology. Pathology. Brazil.

RESUMO

As características histológicas da insuficiência hepática fulminante foram correlacionadas com os achados demográficos, clínicos, bioquímicos e virológicos, em crianças e adolescentes nativos do Estado do Amazonas no Norte do Brasil. 96,2% tinham evidência de infecção primária pelos vírus hepatotrópicos primários. A análise histológica revelou três padrões histopatológicos distintos de insuficiência hepática fulminante.

Palavras-chaves: Hepatite. Insuficiência hepática fulminante. Epidemiologia. Patologia. Brasil.

Several studies have characterized the Brazilian Amazon basin as a high endemic area for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) infection[12,13,16], and Yellow fever virus[3]. In this region, an unusual type of fulminant hepatic failure, known as Labrea Fulminant Hepatitis, has been documented in the Brazilian territory of the Amazon Basin[4,9,14,17,18]. First described over 50 years ago[8], this disease is characterized by severe hepatitis, coursing within days to hepatic failure and death[4,9,17,18,23]. Children, adolescents and young adults are mainly affected[4,14,18,23].

The availability of histophatological liver specimens from cases of Labrea Fulminant Hepatitis, showing a specific picture of microvesicular steatosis (morula-like cells) and eosinophilic necrosis, has been pointed out by Brazilian authors[9,11]. This pattern is different from those of massive and sub-massive necrosis found in ordinary fulminant viral hepatitis[9,11]. Similar clinical and histological features of Labrea Fulminant Hepatitis have been found in the Northern and Eastern regions of Brazil[1,22], as well as Northern Colombia[5], Western Venezuela[19], Peru[6] and Central African Republics[21]. One case of non-fatal acute HDV with microvesicular steatosis in a young woman has been reported in the United States[20]. Studies in the Amazonas State (northern Brazil) have demonstrated that 63.6% of patients with Labrea Fulminant Hepatitis presented evidence of infection by HAV, HBV, HCV and HDV, either in isolation or simultaneously[14].

The purpose of the present retrospective study was to correlate the histological findings of fulminant hepatic failure with the demographical, clinical, biochemical and virological features in children and adolescents, native to the Amazonas State.

We reviewed 23 patients admitted to our hospital between January 1984 and March 2002. A 10-mL blood sample was collected from all patients at admission, then centrifuged, aliquoted, and stored at –70°C. Sera from these patients (13 males, 10 females; aged 3 - 18 years; mean 12.5 years), with post-mortem histopathological diagnosis of fulminant hepatic failure were screened for the presence of: HAV (anti-HAV IgM); HBV (HBsAg,

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Recebido para publicação em 5/11/2002
Aceito em 18/12/2003

anti-HBc IgM); HDV (HDAg, total anti-HD IgG, anti-HD IgM) with standardized ELISA assay (Hepanonostika, Organon Teknika^{R}, B.V. Holland; and Diasorin^{R}, Saluggia, Italy). The HBV-DNA, HCV-RNA, HDV-RNA, HEV-RNA and HGV-RNA were tested with an in-house nested polymerase chain reaction (PCR). The HCV-RNA was also investigated in sections of liver by PCR, from 4μm-thick microtome shavings of blocks of the paraffin-embedded tissues using a modification of the technique described elsewhere[24]. Antibodies to yellow fever (MAC-ELISA IgM) were investigated in serum from patients with histological diagnosis suggestive of yellow fever. Autopsy samples of liver tissue were obtained from 23 patients who died with a clinical and laboratorial picture of fulminant hepatic failure. Tissue samples were fixed in formalin, routinely processed in Auto-Technicon (Technicon Co, USA) and embedded in paraffin blocks; 4μm-thick sections were submitted to impregnation of the reticulin frame work by silver and stained by Hematoxylin and Eosin. Liver function tests, including alanine aminotransferase (ALT), were performed using automated routine laboratory procedures. The study was approved and authorized by the local Ethics Committee.

According to the histopathological aspects of the liver, the patients (see Table 1 for characteristics of patients at baseline by liver histology) were classified into three groups.

Group 1 . Ten (44.4%) patients showed diffuse microvesicular steatosis (morula-like cells), lytic and eosinophilic necrosis (5 males, 5 females; aged 3 - 18 years, mean 10.8 years), without evidence of massive or sub-massive necrosis. The time between the first clinical manifestations and death ranged from 2 to 8 days (mean 4.6 days). The mean value of ALT was 1,983 U/L. On the basis of serological tests, 4 (40%) had acute or reactivation of an existing HBV infection (HBsAg^{+}, anti-HBc IgM^{+}, HBV-DNA^{+}), 2 (20%) had HBV/HDV coinfection (HBsAg^{+}, anti-HBc IgM^{+}, HBV-DNA^{+}, anti-HD IgM^{+}), 2 (20%) had HDV superinfection in chronic HBV carriers (HBsAg^{+}, total anti-HBc^{+}, anti-HD IgM^{+} or HDV-RNA^{+}), 1 (10%) had HAV infection (anti-HAV IgM^{+}) and 1 (10%) probably HCV superinfection in chronic HBV carrier (HCV-RNA^{+} in liver tissue and HBsAg^{+}, total anti-HBc^{+} in the serum). Morula-like cells were more frequently found in HDV acute superinfection in chronic HBV carries.

Group 2 . Eleven (47.8%) patients showed massive or submassive necrosis (6 males, 5 females; aged 3 - 17 years, mean age 13.5 years), without evidence of morula-like cells. The time between the first clinical manifestations and death ranged from 4 to 31 days (mean 10.2 days). The mean value of ALT was 2,229U/L. In this group, 4 (36.3%) had HDV superinfection in chronic HBV carriers (HBsAg^{+}, total anti-HBc^{+}, anti-HD IgM^{+} or HDV-RNA^{+}), 3 (27.2%) had HBV+HDV coinfection (HBsAg^{+}, anti-HBc IgM^{+}, HBV-DNA^{+}, anti-HD IgM^{+}), 2 (18.1%) had HAV infection (anti-HAV IgM^{+}), 1 (9.2%) had HAV/HBV coinfection (anti-HAV IgM^{+}, HBsAg^{+}, anti-HBc IgM^{+}, HBV-DNA^{+}), and 1 (9.2%) was negative to HAV, HBV, HCV, HDV, HEV and HGV markers.

Group 3 . Two (9.5%) patients showed midzonal coagulative necrosis (2 males, aged 14 and 18 years), with positive Yellow Fever IgM in both.

Our study demonstrates that 95.6% of children and adolescents with fulminant hepatic failure presented evidence of infection by primary hepatotropic viruses. These results are similar to those observed among children and adolescents in India (72.5%)[2]. On the other hand, our results differ from the findings among children and adolescents of developing countries where the prevalence of fulminant hepatic failure caused by primary hepatotropic viruses is very low (15%)[10]. Infection by HBV, either alone or associated with HDV or HAV, is the major pathogenic determinant in fulminant hepatic failure. In our series only one patient (4.3%) had an inconclusive diagnosis.

A high percentage was observed of coinfection or superinfection by primary hepatotropic viruses (HAV, HBV, HCV, HDV) in our patients (65%). This observation has been documented in endemic areas for HAV, HEV, HBV, HDV infection[2 11 15 16], and the associated infection possibly explains the clinical severity and biochemical abnormalities found in fulminant hepatic failure. In our casuistic, the probable acute C hepatitis (HCV genome present in the liver tissue) can lead to fulminant hepatic failure in chronic HBV carriers (HBeAg and HBV-DNA negative in the serum). These results confirm previous findings that acute HCV superinfection can cause severe liver injury in chronic carriers of hepatitis B virus[7].

Three distinct histological patterns of fulminant form of hepatitis were observed in children and adolescents of Amazonas State, of these, two were linked to primary hepatotropic virus, regardless of its etiology, and the other related to classic Yellow fever. These data differ from data described in the literature, with a classical histopathological pattern of fulminant hepatic failure by hepatotropic viruses: the classic picture of massive or submassive necrosis without evidence of morula-like cells[2 10].

The demographic, clinical, biochemical and virological findings from children and adolescents with microvesicular steatosis (morula-like cells) are not different from those of massive or submassive hepatic necrosis. The microvesicular steatosis (morula-like cells) were found mostly in HDV acute superinfection, as well

Table 1 - Patients characteristics at baseline (liver histology).

	Histogical findings		
Characterististics	presence of "morula-like" cells	classic fulminant hepatitis	yellow fever
Number of patients	10	11	02
Sex (male/female)	(5/5)	(6/5)	(2/0)
Mean age (in years) and range	10.8 (3-18)	13.1 (3-17)	16.0 (14-18)
Mean values of ALT* and range	1,983 (310 - 6,500)	2,229 (760 - 9,413)	3,949 (520 - 7,378)

*ALT, Alamine aminotransferase (normal range 20-65 IU/L)

as in HAV/HBV acute coinfection and probably HCV acute superinfection in chronic HBV carriers. Extensive studies, including sequencing of HBV and HDV (viral genotype), are necessary to better understand whether differences in viral mutations could be responsible for severe hepatitis in Northern Brazil. Studies in Peru, found that HBV genotype F and HDV genotype III may be associated with severe cases of acute hepatitis[6]. Based on our results, we conclude that hepatotropic viruses and arboviruses in endemic areas are associated with a substantial risk of fulminant hepatic failure in children and adolescents. Finally, the high prevalence of associated infection may contribute to severe forms of fulminant hepatic failure in children and adolescents in Northern Brazil.

ACKNOWLEDGEMENTS

The authors are deeply grateful to Prof. Leila Pereira (Universidade Federal de Pernambuco), Prof. Mario Rizzetto (University of Turin, Italy), and Prof. Oscar Fay (Instituto Nacional de Microbiologia, Rosário, Argentina), for performing part of the molecular hybridization tests.

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