

Acute liver failure in children: observations in Vitória, Espírito Santo State, Brazil

Insuficiência hepática aguda na criança: observações
em Vitória, Estado do Espírito Santo, Brasil

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Abstract In this communication we report 46 cases of acute liver failure in children diagnosed at the Hospital Infantil Nossa Senhora da Glória in Vitória, E Santo. Serology for IgM anti-HAV, IgM anti-HBc, HbsAg, anti-HCV and biochemical tests were performed in all cases in a routine laboratory. The M/F ratio was 1.1:1 and the mean age was 4.7 ± 3.2 years, without gender difference. Anti-HAV IgM+ in 38 (82.6%) cases, anti-HbclgM+ in two (4.3%) cases and 6 (13.1%) cases were negative for all viral markers investigated. Anti-HCV+ in one anti-HAV IgM+ case. HbsAg+ in two anti-HbclgM+ and in two HAVIgM+ cases. Among the six A, B and C negative cases, four (8.6%) did not have the suspected exogenous intoxication. Mortality was 50%, without gender or age differences. These results demonstrate that HAV infection is the main etiology of acute liver failure in children in Brazil, confirming that, although it is a self limited, relatively mild illness, it can cause serious and even fatal disease. The observation of four cases without A, B and C viral markers and no history of exogenous intoxication, agree with the observation of non A-E acute sporadic hepatitis in Northeastern Brazil.

Key-words: Fulminant hepatitis. Liver failure. Acute hepatitis. Hepatitis A. Hepatitis.

Resumo São relatados 46 casos de insuficiência hepática aguda, diagnosticados no Hospital Infantil Nossa Senhora da Glória, em Vitória, Espírito Santo. Sorologia para IgM anti-HAV, IgM anti-HBc, HbsAg, anti-VHC e testes bioquímicos realizados em laboratório de rotina. Relação M/F de 1,1:1; média de idades: $4,7 \pm 3,2$ anos, sem diferença entre os sexos. IgM anti-VHA+ em 38 (82,6%) casos, IgM anti-HBc+ em dois (4,3%) casos e seis (13,1%) casos foram negativos para os marcadores virais investigados. HbsAg+ em dois casos IgM anti-HBc+ e em dois com IgM anti-VHA+. Anti-VHC+ em um caso IgM anti-VHA+. Entre os seis casos negativos para VHA, VHB e VHC, quatro (8,6%) não tinham suspeita de intoxicação exógena. A mortalidade foi de 50% sem diferenças em relação à idade ou sexo. Os resultados demonstram que o vírus da hepatite A é o principal agente etiológico de insuficiência hepática aguda em crianças no nosso meio. A observação de quatro casos sem marcadores para infecção com os vírus A, B ou C e sem suspeita de intoxicação exógena está de acordo com o relato de hepatites agudas esporádicas não A-E no Nordeste do Brasil.

Palavras-chaves: Hepatite fulminante. Insuficiência hepática. Hepatite aguda. Hepatite A. Hepatite.

Acute liver failure or fulminant hepatitis in children is defined as the development of hepatic encephalopathy within 4 or 8 weeks after onset of jaundice^{1,4,10}. Worldwide the most common causes of acute liver failure in children are acute viral hepatitis and drug-induced hepatocellular injury. However there are few reports dealing with the etiology of this syndrome in developing countries and especially in Latin America.

Zacarias et al¹⁹ reported 71% of HAV IgM, 14.2% of HBV IgM and 14.2% negative for HAV or HBV among

28 children with acute liver failure diagnosed in Santiago, Chile. Similar high frequency of HAV among 70 children with acute liver failures was reported in Buenos Aires by Ciocca⁴: 64% HAV, 5% HBV and 28% negative for HAV and HBV, the last cases being considered cryptogenic.

In Brazil there are few reports about the etiology of acute liver failure in children. In the Brazilian part of Amazon Basin acute liver failure in children and young people frequently has the pattern of Labrea fever (fulminant hepatitis with microvesicular steatosis or

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spongiform hepatitis) and is related to HDV, HBV and HAV infection, alone or in association^{6,7}. Isolated cases of fulminant hepatitis with microvesicular steatosis (spongiform hepatitis) in children have been reported in Northeast and Southeast Brazil^{2,11,13}.

PATIENTS AND METHODS

The study is a description of a series of 46 cases of children with acute liver failure, retrieved from 109 records of children with diagnosis of acute hepatitis, admitted at the Children's Hospital NS da Glória from January 1992 to January 1999. Biochemical tests (total bilirubin, serum albumin, ALT, AST and prothrombin time) and serology for HAV (anti-HAV IgM), for HBV (HbsAg and anti-HBc IgM) and anti-HCV, were done in all cases, using commercial kits in a routine laboratory.

The criteria for inclusion of a case as acute liver failure were laboratory evidence of liver failure (increased bilirubin levels over 2mg/dl and a prothrombin time lesser than 55% of the control, that corresponds to International Normalization Ratio equal or higher than 1.5), associated with signs of hepatic encephalopathy. The encephalopathy was classified according the

Here we report the main epidemiological profile of children with acute liver failure diagnosed at the children's Hospital N. Srª da Glória, in Vitoria, ES, from January 1992 to January 1999, with special attention to viral etiology.

following grades of severity¹⁶: grade 1 (confusion and mood changes), grade 2 (drowsiness and inappropriate behavior), grade 3 (stupor) and grade 4 superficial coma (arousable by simple commands) or profound coma (no responses to any stimuli). Electroencephalogram was used for assessment of encephalopathy in all cases.

Among the 109 children with acute hepatitis, 46 had clinical signs of acute liver failure according the criteria cited above. The data related to age, sex, birthplace, biochemical findings, results of serology for hepatitis virus, duration of illness and evolution from these 46 cases were collected and analyzed.

When necessary the software EPIINFO version 6.1 was used for statistical analysis.

The ethical Committee from the Biomedical Center, Federal University of Espirito Santo approved this research.

RESULTS

The data related to age, gender, birthplace and the results of main biochemical tests and serology of the 46 cases are presented in Table 1. Thirty eight (82.6%) cases were positive for anti HAV, IgM two (4.3%) cases were positive for anti-HBc IgM, six (13.01%) cases were negative for anti HAV IgM, antiHBc IgM and anti-HCV and one (2.17%) case had positive anti HAV IgM and anti-HCV. In this case the identification of HCV RNA was not done. HBsAg was positive in four cases (two positives for antiHBcIgM and two positives for anti-HAV IgM). Two out of six viral negative cases had a history of exogenous intoxication.

Encephalopathy grade 1 was present in 16 cases, grade 2 in 5 cases, grade 3 in 2 cases and grade 4 in 23 cases.

Fatal evolution occurred in 23 (50%) cases. Mortality was 44.7% (17/38) of HAV positive cases, 50% (1/2) of HBV positive cases and 83.33% (5/6) of the HAV, HBV and HCV negative cases. The differences in mortality ratio in regard to the etiology were not significant, although it was higher among cases without positive viral markers.

There were no gender or age differences in children that died (Table 1). The only biochemical parameters that were significantly different in fatal cases were prothrombin time and serum albumin level (Table 1).

DISCUSSION

The Children's Hospital NS da Glória is a reference Hospital for the public health system that attends children of low social-economic status from the different cities of Espirito Santo State. In this series 67.4% of children come from the suburbs of Metropolitan Vitória and 22.6% from other cities. These frequencies did not differ from the origin of children that are admitted to the Hospital because of other diseases.

The male female ratio (1.1:1) and mean age (5.2±3.4 years) were similar to that observed in Santiago¹⁹.

The high frequency of acute liver failure associated to acute hepatitis A is similar to the observed in Santiago¹⁹, Buenos Aires⁴ and Pakistan¹⁵. In the developed countries acute liver failure in children is more frequently associated to HBV infection or exogenous intoxication¹³ with rare cases of acute liver failure in children due to HAV infection⁵.

The occurrence of four cases (8%), without a history of exogenous intoxication and with negative serology for both anti-A IgM and anti HBc IgM indicates the possibility of existence of acute liver failure in children caused by nonA-E hepatitis in Vitoria. This observation is in agreement with the observation of high frequency of non A-E acute sporadic hepatitis in Northeastern Brazil¹².

The frequency of fatal evolution (23/46; 50%) was similar to that reported in acute liver failure in children in developing countries^{4,15,19}, but less than that observed in developed countries, where viral etiology is less frequent^{5,14}. Although without statistic significance, mortality was lower among the cases associated with A or B virus infection than in the cases with negative serology (respectively 18/40 and 5/6; Fisher's exact test, p=0.089).

There was a high frequency of fatal cases among children with HAV infection, similar to that observed in Buenos Aires⁴ (60% died) and in Kanacki, Pakistan¹⁴

Table 1- Age, gender, birth place, results of biochemical tests* and serology for hepatitis A virus (HAV), hepatitis B virus (HBc and HbSAg) and hepatitis C virus (HCV) in 46 children with acute hepatic liver failure diagnosed in Vitória, E Santo, Brazil.

Variables	All	Patients discharges	deceases	p**
Gender (M/F)	23/23	9/14	9/14	0.238
Birth place				
Vitória ^a	31	13	18	-
Other cities	15	10	5	0.208
Viral markers+				
IgMAnti-HAV +/--%	38/8 (82.6%)	21 (55.3%)	17 (44.7%)	-
IgMAnti-HBc +/--%	2/46 (4.3%)	1 (50%)	1 (50%)	-
HbsAg ^b +/--%	4/42 (8.6%)	1 (25%)	3 (75%)	-
Anti-VHC +/--%	1/45 (2.15)	1 (16.7%)	5 (83.3%)	0.089
Viral markers -	6	1	5	-
	mean±SD median	mean±SD median	mean±SD median	
Age (years)	4.7±3.1 4.0	5.4±3.3 4.0	4.1±2.8 4.0	0.136
PT (seconds)	27.4±12.8 21.0	20.2±7.3 17.5	34.6±13.3 38	0.000
Bd (g/dL)	16.2±13.1 11.6	15.5±14.7	16.9±11.4 13.8	0.712
AST*	1317±1614 456	1371±1285 1091	1262±1917 294	0.826
ALT*	989±1149 4665	856±649 740	1124±1498 257	0.444
Albumin (g/dL)	3.1±0.75 3.7	3.6±0.48 3.6	2.7±0.73 3.0	0.005

* Laboratory data represent the mean of the higher value observed in each case until the diagnosis of acute liver failure was established. **p value for the comparison between discharged and deceased patients; χ^2 or Fisher's exact test for proportions and Mann-Whitney test for means. ^a Metropolitan Vitória formed by the cities of Vitória, Vila Velha, Cariacica, Serra and Viana. Bb=Total bilirubin; PT= Prothrombin time; ALT=alanine amino transferase; AST=aspartate amino transferase; *International Units / L. ^b Two cases were IgM anti-A positive and the other two cases were IgM anti-HBc positive, which were included also as IgM-anti-HBc(+) or IgM anti-HAV(+).

(37% died). It is possible that other factors as malnutrition, contributed to high mortality of severe hepatic dysfunction in children with HAV infection in developing countries. However severe HAV infection has been reported in some epidemics in developed countries¹⁸.

Some authors argued that superinfection with HAV in patients with chronic hepatitis C could be a factor for more severe disease, an observation not confirmed by

other investigators^{3 9 17}. Among our patients only one had positive serology for anti-HCV and IgM anti-HAV and this patient survived.

In conclusion our observations demonstrate that HAV infection is the main etiology of acute liver failure in children in our Country, with high mortality, confirming that, although HAV infection is a self limited, relatively mild illness, it can cause serious and even fatal disease⁸.

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