Fulminant acute hepatitis in pediatrics in Latin America and the Caribbean

INTRODUCTION

Fulminant Acute Hepatitis (FAH) is a serious and dynamic clinical syndrome characterized by the quick worsening of hepatic function in patients without a history of liver disease. Both the epidemiology and etiology of FAH are little known, especially in pediatrics. It has several causes, the main ones being acetaminophen poisoning, infections (especially viral ones), metabolic diseases, autoimmune diseases, among others.

The interval between the onset of symptoms and hepatic encephalopathy has determined different definitions for FAH. Although these definitions may differ in some clinical aspects, in clinical practice, they are usually not used. Actually, hepatic en-
Caribbean and identify possible measures aiming at a better understanding and the improvement of the patient support.

**METHODS**

For the selection of the articles analyzed in this review, the PubMed and SciELO databases were searched by three different researchers (JCJ, RT, and FC), as shown in Figure 1.

We included studies of the following modalities: prospective or retrospective cohort, papers of systematic and non-systematic review and clinical trials, case reports, and case series containing a description of patients with HAF with a maximum age of 18 years. Only studies available in Portuguese, English, or Spanish were considered.

In the search mechanisms, the following terms were used: acute OR fulminant AND liver OR hepatic AND failure in the PubMed database and acute liver failure/falla hepática aguda in the SciELO database. We used three filters: for languages (English, Portuguese and Spanish), age (pediatrics), and date of the study (from 2000 up to 2016). All references were checked to decrease the possibility of excluding any relevant studies.

The objective of this review was to investigate the epidemiology of FAH in Latin America and the Caribbean and identify possible measures aiming at a better understanding and the improvement of the patient support.

**TABLE 1 - DISTRIBUTION OF INFECTIOUS FAH PER COUNTRY OF ORIGIN.**

<table>
<thead>
<tr>
<th>Infectious causes</th>
<th>Brasil</th>
<th>Argentina</th>
<th>Chile</th>
<th>Cuba</th>
<th>Others</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>99</td>
<td>268</td>
<td>61</td>
<td>0</td>
<td>11</td>
<td>439</td>
<td>76.9</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>26</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>30</td>
<td>5.3</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0.9</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>2</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>38</td>
<td>6.7</td>
</tr>
<tr>
<td>Hepatitis A + C</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Hepatitis A + B</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Hepatitis B + D</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>1.4</td>
</tr>
<tr>
<td>Chronic Hepatitis B + C</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Chronic Hepatitis B + D</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1.1</td>
</tr>
<tr>
<td>Viral Hepatitis, untyped</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>1.2</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.4</td>
</tr>
<tr>
<td>Dengue</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Herpes</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>CMV</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>145</td>
<td>306</td>
<td>73</td>
<td>13</td>
<td>12</td>
<td>571</td>
<td>100.0</td>
</tr>
</tbody>
</table>
We adopted the following exclusion criteria: duplicate studies, editorials in journals, book chapters, papers retrieved by the search terms but which no relation to the subject of the review, studies in adult patients, experimental studies, and articles not related to the Latin America and Caribbean regions.

The data obtained were entered into tables, and the sum of the columns and the averages were calculated. The chi-square test and the Student’s t-test were used for statistical analysis.

RESULTS

We found 2,879 articles in the databases searched. After the initial selection, we evaluated the titles or abstracts and removed 2,785 papers based on the exclusion criteria; a total of 92 publications were left for evaluation. After further verification, we excluded another 24 articles (8 duplicates and 16 not related to the topic of the study). As a result, there were 68 remaining studies for analysis.

Of the studies analyzed, 34 were published in international journals and 34 in national journals of their respective countries. In total, we evaluated FAH 1,265 cases, with a predominance in females (42.9%), followed by males (39.4%); in 17.7% of cases, there was no description of sex.

The virus, especially those of hepatitis, were the main causes for ALF, in 45.1% of the cases. The hepatitis A virus was responsible for 34.7% of the total
number of cases and 76.9% of infectious causes. Other viruses such as parvovirus, herpes, cytomegalovirus, Epstein-Barr, dengue, and rubella were also described. Of the total of patients, 340 (26.9%) were described as idiopathic, and 145 (11.5%) had no cause described. Table 1 shows the distribution of infectious HAF per country of origin.

We found 62 cases (4.9%) of autoimmune diseases, and poisoning accounted for 3.4% of cases, the most common being poisoning by fireworks (27.9%), followed by the use of isoniazid (16.3%). Paracetamol was reported in only 0.2% of all cases of ALF and in 4.6% of the drug causes.

The countries that had the most published articles on FAH were Brasil (30.4%), Chile (24.3%), and Argentina (18.8%). Reports were also found from the following countries: Peru, Uruguay, Colombia, Costa Rica, Mexico, and Cuba.

Other data found also refers to the number of deaths and transplant patients. There were a total of

### TABLE 2 - MAIN ALF STUDIES IN LATIN AMERICA AND THE CARIBBEAN.

<table>
<thead>
<tr>
<th>Author/Country</th>
<th>Objective</th>
<th>Intervention</th>
<th>Controls</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreira-Silva et al. 2016, Brasil</td>
<td>Description of a series of ALF cases in children</td>
<td>None</td>
<td>Evaluated biochemical and serological tests of patients</td>
<td>46 patients</td>
<td>38 patients with hepatitis A, 2 cases with hepatitis B, and 6 cases with no diagnosis; mortality of 50%</td>
</tr>
<tr>
<td>Uribe et al. 2008, Chile</td>
<td>Analysis of epidemiology and outcomes of LT in ALF in Chile</td>
<td>LT in patients from the waiting list for liver transplantation in the country</td>
<td>Use of steroids, cyclosporine, and azathioprine, with the use of mycophenolate, and tacrolimus in some cases.</td>
<td>42 patients, 27 submitted to LT</td>
<td>27 patients with LT: 13 females; 1 male; 10 with hepatitis A; 3 autoimmune; 12 cryptogenic; 7 died after LT, with 3 unsuccessful retransplantations; 20 patients were discharged with 5-year follow up after the procedure and survived</td>
</tr>
<tr>
<td>Cuarterolo et al. 2009, Argentina</td>
<td>The child evolution during the first year after LT</td>
<td>All patients received cyclosporine</td>
<td>Periodic examinations during the first year after LT</td>
<td>143 patients</td>
<td>Of the 143 patients, 14 needed retransplantations</td>
</tr>
<tr>
<td>Ciocca et al. 2010, Argentina</td>
<td>Study the etiology, outcome, and prognosis in children with ALF</td>
<td>None</td>
<td>Patient follow up until hospital discharge, death, or LT</td>
<td>215 patients, but only 210 with medical records</td>
<td>128 patients with hepatitis A, 68 indeterminate, and 13 of other causes; 59 survived with hospital discharge and no LT, 61 died and 90 received LT</td>
</tr>
<tr>
<td>Ferreira et al. 2005, Brasil</td>
<td>Retrospective report of the last 10 years of children with ALF due to hepatitis A</td>
<td>None</td>
<td>Evaluated biochemical and serological tests of all patients</td>
<td>33 patients</td>
<td>13 patients were positive for hepatitis A, 11 had no cause determined, 1 had a spontaneous recovery, 5 died before LT, 7 underwent LT with total survival after 4 patients (1 with no LT and 3 without after LT)</td>
</tr>
<tr>
<td>Roque et al. 2009, Chile</td>
<td>Report the experience of a LT center</td>
<td>LT</td>
<td>Evaluated biochemical and serological tests of all patients</td>
<td>8 patients undergone LT between 1997 and 2008</td>
<td>5 patients received LT from a dead donor; 5 female patients; 3 had kidney failure, with 2 deaths among the 8 patients</td>
</tr>
<tr>
<td>Sotelo et al. 2009, Mexico</td>
<td>Description of early use in patients with ALF secondary to hepatitis A</td>
<td>Treatment with N-Acetyl Cysteine for patients with ALF secondary to hepatitis A</td>
<td>Clinical symptoms and biochemical tests.</td>
<td>12 patients with ALF, of 72 patients with hepatitis A</td>
<td>6 males; 6 females – 9 patients received oral treatment and 3 through nasogastric intubation. Average treatment for 15 days, with one case needing more 15 days</td>
</tr>
<tr>
<td>Uribe et al. 2013, Chile</td>
<td>Analysis of epidemiology and outcomes of LT in ALF</td>
<td>LT in patients from the waiting list for LT in the country</td>
<td>Hospital protocol of immunosuppression regimen</td>
<td>189 patients</td>
<td>230 LT performed; ALF etiology was unknown in 50% of cases, 68% of the patients had 10-year survival, with 90% in the last 3 years</td>
</tr>
<tr>
<td>Silverio et al. 2015, Cuba</td>
<td>Describe the outcome of children with ALF in Cuba</td>
<td>None</td>
<td>Evaluated biochemical and serological tests of all patients</td>
<td>31 patients</td>
<td>61% of the cases were infectious, 41% by cytomegalovirus; spontaneous recovery in 48% of cases (19); only 3 received LT and 13 died</td>
</tr>
<tr>
<td>Tannuri et al. 2016, Brasil</td>
<td>Results of LT before and after living donor LT became possible, starting in 2007</td>
<td>Living and dead donor LT in ALF patients</td>
<td>Clinical symptoms and biochemical tests.</td>
<td>115 patients</td>
<td>48 of the 115 patients with LT indication before the institution started performing living donor transplantation, 67 after; 48% mortality after LT, with greater incidence in patients who received LT from a dead donor; 64.3% before 2007 and 50% after; 45% with undefined etiology</td>
</tr>
</tbody>
</table>

ALF: Acute Liver Failure; LT: Liver Transplantation.
326 deaths reported (25.8% of cases) and 634 transplant patients (50.1% of cases).

The main studies, with their objectives, number of patients, and results are listed in Table 2.

**DISCUSSION**

This is the first review of the epidemiological aspects of FAH in the Latin America and Caribbean regions. With the results obtained, we evaluated the importance of VH in the causes of ALF. Although some of them are preventable by vaccination, VHs are the main infectious agents that cause FAH in the regions assessed, representing 94.3% of all cases described in this study, followed by yellow fever (2.3%), and cytomegalovirus (1.5%).

FAH secondary to VH has as its predominant cause the type A virus (HAV), representing 76.9% of all infectious causes; Argentina alone is responsible for 61.0% of all HAV cases. This reality seems to be changing after the introduction of HAV vaccination on a large scale in the country in 2005. Since 2006, there was a 88.1% decrease compared to the period prior to the vaccination. Also were also no cases of FAH not notified in the country, nor the need for liver transplantation due to HAV since March 2007.

It should be noted that, way behind HAV infection, there are also infections by the type E virus (6.7%), and type B (5.3%), which could indicate the effectiveness of the Type B VH vaccination, which used to be more prevalent and nowadays is a rare cause of FAH.

The country with the highest number of cases described was Argentina, with 53.6% of all infectious HAF, followed by Brasil (25.4%), and Chile (12.8%). These data lead to the question: Do these numbers reflect the reality in these regions studied or just the publication capacity of researchers from each country? Regardless, these data provide important information on the causes of FAH in Latin American and Caribbean countries with potentially preventable diseases, thus providing the possibility of planning effective measures that can contribute to the reduction of morbidity and mortality.

Among the drug or poisoning causes, we found a different reality from the one reported in other countries such as the United States and the United Kingdom, where paracetamol is the main agent of drug-induced FAH and mushrooms can cause enough poisoning to produce FAH. In Latin America and the Caribbean, paracetamol appeared in only two out of a total of 43 cases. Surprisingly, fireworks were the main etiology of FAH in patients suffering from exposure to its chemical agents, especially yellow phosphorus.

Considering the other causes, a considerable number of FAH cases due to autoimmune diseases appears in this review. There were 62 cases (4.9% of the total), and Brasil (28 cases) and Argentina (16 cases) were responsible for the majority of the cases reported. There is also a large number of cases classified as idiopathic. There was a total of 340 cases classified this way (26.9% of the total), in addition to 145 cases with no cause described, which proves the difficulty of performing more complex etiological diagnosis in the pediatric age range, only notifying the most common infectious causes.

Another important data found in this study concerns the outcome of FAH cases submitted to liver transplantation (LT). Only half of the patients (50.1%) was submitted to LT, which might reflect the low mortality rate found (25.8% of cases).

Considering the population of the regions studied (Latin America and the Caribbean), we found a number of articles below expected, comprised mostly of case reports or case series and regional studies in a single center. We noticed the absence of multicenter studies of greater impact, which could best contribute to the review.

**CONCLUSION**

The avoidable causes of Fulminant Acute Hepatitis in Latin America and the Caribbean include the hepatitis viruses — especially hepatitis A — and poisonings. The active vaccination, basic sanitation, and public awareness can reduce the number of FAH patients and, consequently, the costs with the LT due to these causes. Paracetamol does not represent an emerging cause of FAH in this region, according to this review. Moreover, the high number of patients with idiopathic HAF or with no cause described draws attention and should guide public health efforts for the better elucidation of the epidemiology of FAH.

**Acknowledgments**

We thank Paola Pitta, who collaborated in the database search stages, and Simone Isidoro Prado, who collaborated with the elaboration of Figure 1.
RESUMO

OBJETIVO: O objetivo desta revisão foi investigar a epidemiologia da hepatite aguda fulminante na América Latina e Caribe e identificar possíveis ações objetivando melhor compreensão e melhora do suporte desses pacientes.


RESULTADOS: Foram encontrados 2.879 artigos nos bancos de dados pesquisados. Após seleção e exclusão de artigos de acordo com o protocolo de pesquisa, ressaltaram 68 estudos remanescentes para análise. Foram avaliados 1.265 casos com hepatite aguda fulminante, havendo predominância no sexo feminino (42,9%), seguido do masculino (39,4%), sendo que não houve a descrição de sexo em 17,7% dos casos. A principal causa foram as hepatites virais (HV), representando 45,1% dos casos. O vírus da hepatite A foi responsável por 34,7% do total de casos e por 76,9% dos causas infecciosas. Do total de pacientes, 26,9% foram descritos como idiomáticos e 11,5% não tiveram causa descrita.

CONCLUSÃO: As causas evitáveis de hepatite aguda fulminante incluem os vírus da hepatite — principalmente o vírus da hepatite A — e intoxicações. A vacinação ativa, o saneamento básico e a conscientização pública podem reduzir o número de doentes e, consequentemente, os custos com transplante hepático por essas causas.


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