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GENARIO OLIVEIRA SANTOS JÚNIOR

FREQUÊNCIA DE HEPATITE FULMINANTE POR MEDICAMENTOS ALOPÁTICOS, FITOTERÁPICOS, INSUMOS VEGETAIS E COMPLEMENTOS ALIMENTARES EM CENTROS DE REFERÊNCIA NO BRASIL.

DISSERTAÇÃO DE MESTRADO

Salvador
2014

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Dissertação apresentada ao Programa de Pós-Graduação em Medicina e Saúde, da Faculdade de Medicina da Bahia, Universidade Federal da Bahia, como requisito para a obtenção do grau de Mestre em Medicina e Saúde.

Orientador: Prof. Dr. Raymundo Paraná
Coorientadora: Prof.ª Dr.ª Lúcia Noblat

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Salvador, Bahia

Dedico este trabalho aos meus pais, Genário e Joselita, exemplos de coragem e força .

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SANTOS JÚNIOR, Genario Oliveira. **Frequency of fulminant hepatitis allopathic, herbal, vegetable supplies and food supplements in reference centers in Brazil**. 62 f. 2014. Thesis (MS) - Federal University of Bahia. Faculty of Medicine.

ABSTRACT

Fulminant hepatitis or fulminant hepatic failure is characterized by rapid loss of liver function. It has different metabolic etiologies, especially viral hepatitis and drug-induced liver injury (DILI) . According to WHO in a period of 35 years fulminant hepatic failure related to DILI has been reported mainly by the use of drugs, such as paracetamol, flutamina, herbal medicines , herbs and halothane . Although case reports of severe DILI are frequent in many countries, there are few data on the epidemiology of severe DILI in Brazil. **OBJECTIVE**: To determine the frequency of cases of fulminant hepatitis DILI in Brazil. **METHODS**: Retrospective multicenter study. A survey was sent by electronic mail to each center, asking about: operating time of the unit, number of transplants performed, number of fulminant hepatitis and their causes. Subsequently, each center was visited to review the medical files. **RESULTS**: Up to now, of the 60 centers invited, only 05 Liver Transplant Centers (HSC) responded to the survey . From these, 51 cases of Fulminant Hepatitis were evaluated. From these, 33 % (17 /51) were identified as possibly DILI. Non- steroidal Anti-inflammatory drugs (NSAIDs) were the most frequent cause of therapeutic class Fulminant hepatitis. Paracetamol was reported in only one case. Two herbal medicines were identified as the cause of liver injury. **CONCLUSION**: These preliminary data points that DILI epidemiology in Brazil strongly from US and Europe data.

Keywords: Fulminant hepatic failure. Fulminant hepatitis. Hepatotoxicity.

SANTOS JÚNIOR, Genario Oliveira. **Frequência de hepatite fulminante por medicamentos alopáticos, fitoterápicos, insumos vegetais e complementos alimentares em centros de referência no Brasil.** 62 f. 2014. Dissertação (Mestrado) - Universidade Federal da Bahia. Faculdade de Medicina.

RESUMO

A insuficiência hepática aguda ou hepatite fulminante caracteriza-se pela rápida perda da função hepática. Tem diversas etiologias metabólicas, destacando-se as hepatites virais e a hepatite induzida por drogas (DILI). De acordo com a O.M.S. no período de 35 anos a insuficiência hepática fulminante relacionada a DILI tem sido relatada principalmente pelo uso de medicamentos, tais como: paracetamol, flutamina, medicamentos fitoterápicos, insumos vegetais e halotano. Embora os relatos de casos de DILI graves sejam frequentes na literatura, poucos são os dados sobre a epidemiologia da DILI grave no Brasil. **OBJETIVO**: Conhecer a frequência de casos de hepatite fulminante por medicamentos no Brasil. **MÉTODO**: Estudo transversal retrospectivo multicêntrico. Foi enviado um inquérito por correio eletrônico para cada Centro, perguntando sobre: o tempo de serviço, número de transplantes realizados, número de hepatites fulminantes e suas respectivas etiologias**.** Posteriormente, cada centro foi visitado para avaliação dos prontuários. **RESULTADO:** Dos 60 Centros convidados, apenas 05 Centros de Transplante Hepático (C.T.H.), responderam ao inquérito. Foram identificados 51 casos de Insuficiência Hepática Fulminante, 33% (17/51) foram secundários à DILI, destes 02 casos foram secundários ao uso de insumos vegetais. **CONCLUSÃO:** Os dados preliminares da epidemiologia de DILI no Brasil, são semelhantes aos dados dos Estados Unidos e da Europa.

Palavras-Chave: Insuficiência hepática fulminante. Hepatite fulminante. Hepatotoxicidade.

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1 INTRODUÇÃO

O fígado é um órgão com limitado reperrtório de respostas aos seus agravos. Irrigado pela veia porta torna-se o local prioritário no metabolismo de substâncias xenobióticas. Diante de um agravo tóxico, o figado pode ser comprometido e a sua função de excreção biliar, sofrer processo necro-inflamatório ou ainda a apoptose[1].

A insuficiência hepática reflete o grave comprometimento da função hepática devido a uma agressão crônica e persistente ao orgão, permeado com frequência, por episódios distintos e repetitivos de exacerbação do dano parenquimatoso [2].

As características clínicas da insuficiência hepática (I.H.) podem ser evidenciadas pela icterícia, hipoalbuminemia, coagulopatia, coagulação intravenosa disseminada, hiperamoniemia, maiores níveis séricos das enzimas hepáticas LDH (lactato desidrogenase), TGP (Transaminase Glutâmico-Pirúvica), TGO (Transaminase Glutâmico Oxalacética), encefalopatia hepática, síndrome hepatorrenal e coma[3].

A insuficiência hepática quando progride desde o início dos sintomas com encefalopatia hepática, num período de duas a três semanas, pode ser caracterizada como insuficiência hepática fulminante (I.H.F.). Esse padrão é relativamente incomum sendo principalmente causados por hepatite viral fulminante (50% a 65% dos casos) e toxicidade medicamentosa ou química (25% a 30%) [3].

De acordo com a O.M.S. (Organização Mundial da Saúde) no período de 35 anos, foram notificados para o Centro de Uppsala-Suécia, 4.690 casos de hepatotoxicidade; destes, 50 casos evoluíram para insuficiência hepática fulminante, tendo como agentes etiológicos medicamentos mais comuns: o paracetamol, flutamina, halotano e lamivudina e sulfametoxazol^{+} trimetoprima. Nesse mesmo estudo verificou-se que os países com maior número de notificações foram: Estados Unidos, Reino Unido, Alemanha[4]. Paralelamente, a IHF por fitoterápicos, medicamentos naturais e Insumos Vegetais tem sido cada vez mais relatada na literatura.

Estima-se que 5-7% de todos os transplantes nos Estados Unidos da América sejam realizados por I.H.F. Apesar da gravidade, atualmente a sobrevida alcança 46 a 89%[5]. Segundo Andrade Col., dos 461 casos de hepatotoxicidade em Centros de referência na Espanha, em um período de dez anos, 11,7% dos casos levaram ao transplante hepático, ou à morte. Esse mesmo

autor refere que os fatores de risco associados à hepatite fulminante encontrados foram: sexo feminino, intensidade do dano hepatocelular e elevação de bilirrubina [6].

No Brasil, de uma população de 1.622 casos, 30% foram casos de hepatite fulminante e destes, 16% foram ocasionados por fitoterápicos ou insumos vegetais, embora esses percentuais sejam subnotificados [10].

De acordo com os dados da Associação Brasileira de Transplante de Órgãos (A.B.T.O), foram realizados no Brasil no ano de 2012, 1.712 transplantes, sendo que 12% foram em pacientes pediátricos (204/1.712). Em média, o custo do transplante hepático por paciente é de US$ 20.605,0, no Brasil. Sabendo que as reações adversas a medicamentos dose-dependentes podem ser previsíveis, conhecer os medicamentos potenciais como os hepatotóxicos podem prevenir o aparecimento de I.H.F. por medicamentos, bem como reduzir os custos da saúde pública com procedimentos que poderiam ser prevenidos.

Considerando que o uso de medicamentos alopáticos e associado à prática da automedicação, é prevalente em ampla faixa populacional brasileira, associado ao grande consumo de plantas e fitoterápicos, torna-se relevante a investigação da frequência de hepatotoxicidade destas etiologias e sua posterior divulgação para prevenção de riscos à saúde da população. Portanto, o objetivo deste estudo é conhecer a frequência de hepatite fulminante no Brasil por medicamentos alopáticos, fitoterápicos, insumos vegetais e suplementos alimentares**.**

2 OBJETIVOS

2.1 PRINCIPAL:

Determinar a frequência de casos de hepatite fulminante por medicamentos alopáticos fitoterápicos, insumos vegetais e complementos alimentares em Centros de alta complexidade em hepatologia no Brasil.

2.2 ESPECÍFICOS:

Avaliar o perfil de distribuição das etiologias de Insuficiência Hepática Fulminante da população brasileira.

Determinar o perfil de reações hepatotóxicas na população brasileira em pacientes dos Centros de alta complexidade.

3 METODOLOGIA

Estudo multicêntrico retrospectivo, realizado em Centros de Transplante Hepático (C.T.H.) no Brasil. Inicialmente, Todos os Centros de Transplante do Brasil, um total de 60 equipes de transplante em atividade, foram convidados a participar do Estudo. Um convite formal foi encaminhado, por correio eletrônico, pela equipe do Estudo e pela Sociedade Brasileira de Hepatologia. Os convites foram enviados no período de setembro a novembro/2011. Para ter acesso ao endereço eletrônico dos membros dos C.T.H., foi solicitado à A.B.T.O., o contato das equipes.

Para os Centros que aceitaram em participar, foi enviado por correio eletrônico um inquérito, em que foi questionado sobre o tempo de serviço, nome do coordenador do Centro de Transplante, número de transplantes realizados, número de hepatites fulminantes e suas respectivas etiologias. Foi estabelecido um prazo de dois meses para o envio do inquérito respondido, pelos C.T.H. Para aqueles que não responderam naquele período, foi realizado o contato por telefone para confirmar o interesse em permanecer no estudo, em caso positivo era estabelecido um novo prazo de entrega.

Após o Coordenador do Serviço de Transplante convidado ter enviado por correio eletrônico o inquérito devidamente preenchido, foi agendada a visita ao C.T.H. para a apresentação do projeto, a assinatura de Termo de Compromisso na participação e sigilo do estudo, confirmação dos casos apontados no inquérito inicialmente e coleta de dados em prontuário dos pacientes que tiveram como etiologia I.H.F, após o uso de um medicamento, ou de um fitoterápico, ou de insumo vegetal ou de um suplemento alimentar.

Para a coleta de dados em prontuário, utilizou-se um formulário previamente validado, sendo coletadas as informações sociodemográficas, as informações sobre o internamento na unidade hospitalar, os dados laboratoriais, resultados das sorologias virais, marcadores para autoanticorpos, diagnóstico de imagem e biópsia. Foi levantada toda a história medicamentosa, levando em consideração o uso de vegetais, fitoterápicos e complementos alimentares, além da possibilidade de interação medicamentosa quando feito uso de associações de medicamentos e/ou fitoterápicos, insumos vegetais e complementos alimentares. Para os medicamentos alopáticos foi utilizada a classificação da O.M.S., *Anatomical Therapeutic Chemical Code* (A.T.C.).

Para os casos que tiveram internação prévia em outra Unidade de Saúde, e que tivesse informações importantes para elucidação do caso, foi solicitado ao coordenador responsável pelo projeto, do respectivo Centro, que providenciasse o acesso ao prontuário da unidade, para que fosse finalizada a coleta de dados.

Critérios de Inclusão: foram incluídos todos os pacientes atendidos nos Centros de Transplante que tiveram diagnóstico de Hepatite Fulminante e indicação de transplante, segundo os critérios do Hospital do King's College (O'Grady et al., 1989), considerando que: para IHF causada por paracetamol: pH < 7,3 (independente de encefalopatia), ou tempo de protombina > 100 segundos, creatinina > 3,4 e encefalopatia Grau III/IV. Para todas as outras etiologias: Tempo protrombina > 50 segundos, Idade < 10 ou > 40 anos, tempo icterícia-encefalopatia > 7 dias, bilirrubina > 17 mg/ dL.

Para a seleção dos pacientes a serem incluídos no estudo, foi solicitado ao Coordenador do C.T.H., que fizesse um corte de cinco anos retrospectivos em sua lista de transplantados, contados a partir da data de recebimento do inquérito, e que selecionassem todos os pacientes que tiveram o diagnóstico de I.H.F.

Critérios de exclusão: foram excluídos os casos que não possuíam as informações sobre a história medicamentosa prévia à admissão, ausência dos resultados das sorologias virais e marcadores de autoanticorpos e pacientes sem resultado de biópsia.

Para os casos que foram identificados como agente etiológico um fitoterápico ou vegetal, foram consultadas as bases de dados: MOBOT (Missouri Botanical Garden), KEW Gardens (Royal Botanic Gardens), Web of Science, Scopus, Medline, Scielo e Lilacs.

O projeto foi aprovado pelo Comitê de Ética do Hospital Universitário Prof. Edgard Santos. Para os demais Centros de transplantes participantes, foi realizado o procedimento de submissão e aprovação. Cada Coordenador do C.T.H., recebeu dos respectivos Comitês de Ética, toda a documentação necessária do projeto, conforme as recomendações da Plataforma Brasil.

A amostra do estudo foi de conveniência. Para a análise estatística foi utilizado o SPSS 18.0, sendo utilizada para a análise de dados a estatística descritiva.

4 ARTIGOS DE REVISÃO DE LITERATURA

4.1 ARTIGO 1 - FULMINANT HEPATIC FAILURE DUE TO ALLOPATHIC DRUGS, HERBAL MEDICINES, PLANT MATERIALS AND FOOD SUPPLEMENTS IN BRAZIL: LITERATURE REVIEW.

Medicine and Health Postgraduate Program (PPgMS), Faculty of Medicine of Bahia (FMB), Federal University of Bahia (UFBA), Salvador, Bahia, Brazil.

ABSTRACT:

Background: Fulminant hepatic failure (FHF), also known as severe acute hepatitis or hyperacute liver failure is a rapid progression-syndrome. Drug-induced FHF is responsible for approximately 50% of cases in the U.S. This reaction can be predictable and dose-dependent, as exemplified by paracetamol-induced hepatotoxicity, which is the most common cause of FHF. Little is known about the etiology of drug-induced fulminant hepatitis. **Objective**: To verify the frequency of drug-induced fulminant hepatitis in Brazil published in the literature. **Method**: Fifteen original articles reporting on the etiology of fulminant hepatitis in Brazil were reviewed. These articles were obtained from LILACS, SciELO and Medline databases. The following keywords were used: fulminant hepatitis AND Brazil, toxic hepatitis, acute hepatic failure AND Brazil, and "humans" as limiting factor. **Results:** Drug-induced FHF in Brazil is poorly described and few studies were found on their frequency. It was shown that 11% (20/180) of fulminant hepatitis diagnosed were secondary to medication. Valproic acid stands out among the drug causes. Females are the most prevalent gender. No algorithm was used to assess causality in the studies found. **Conclusion:** From the studies found in the literature, it is not possible to determine the frequency of fulminant hepatic failure in Brazil due to DILI (Drug-Induced Liver Injury). More studies are required to better understand the frequency and other potential toxic etiologic agents.

Keywords: fulminant hepatitis; severe hepatic failure; hepatotoxicity.

INTRODUCTION

Fulminant hepatic failure (FHF), also known as severe acute hepatitis or hyperacute liver failure is a rapid-progression syndrome developing into an acute and severe injury and leading to coagulopathy and encephalopathy in patients without any prior liver disease. This is a multiple-etiology disease, with mainly viral and drug-related etiologies, the latter also known as DILI[1].

The latest definitions recognize distinct phenotypes of the disease and quantify the time interval between the onset and development of encephalopathy symptoms[2].

FHF reflects the global destruction of the liver's function due to an insidious action of a progressive chronic disorder through different and repetitive episodes of a parenchymal injury or through sudden and massive obliteration[3].

HF's traits can be evidenced by jaundice, hypoalbuminemia, coagulopathy, disseminated intravascular coagulation, hyperammonemia, higher serum levels of LDH (lactate dehydrogenase) liver enzymes, GPT (glutamic-pyruvic transaminase), aspartate aminotransferase (glutamic-oxaloacetic transaminase), hepatic encephalopathy, hepatorenal syndrome and coma[4].

While unfolding, as from onset of symptoms, with hepatic encephalopathy within two to three weeks, hepatic failure can be characterized as FHF This pattern is unusual and is mostly caused by fulminant viral hepatitis (12%, 25/206) and drug- or chemical-related toxicity (52%, 107/206), with 38% (78/206) paracetamol-related cases. There are many possible etiologies and some cases of unknown etiology. Drugs and chemicals act as direct hepatotoxins or through idiosyncratic inflammatory reactions[4].

According to the World Health Organization (WHO), 4,690 cases of hepatotoxicity were reported to the Uppsala Monitoring Centre, Sweden over a 35-year period (1968-2003). Of these, 50 cases developed to fulminant hepatic failure, whose etiological agents were drugs, such as: paracetamol, flutamine, halothane and lamivudine and trimethoprim-sulfamethoxazole. This study found that countries with the highest number of notifications were: United States, United Kingdom and Germany[5].

It is estimated that 5-7% of all US-based transplants are FHF-related, with 46-89%[6] survival rate. In Europe, 11% of liver transplants are FHF-related[7].

Of the 446 hepatotoxicity cases in Spain's reference centers over a ten-year period, 4% (18/446) of cases led to FHF-related liver transplant, 67% (12/18) of which lead to death. Factors

associated with fulminant hepatitis were: female gender, hepatocellular damage and high levels of bilirubin[8].

In African countries, it was found that of 430 FHF-affected patients, 4.5% (19/430) were drug-related[9]. Another study conducted in the Republic of Sudan demonstrated that 8% (3/37) were secondary to the use of ketoconazole or antituberculostatics[10].

A study in Korea, which recorded all fulminant hepatitis cases during the period 1999-2011, the use of allopathic drugs or herbal medicines were the most common etiologic agent, accounting for 45.2% (19/42) of the cases[11].

In Brazil, few data are available on the epidemiology of hepatic disease induced by drugs or food supplements. In developing countries, drug-induced hepatic disease is much less common and associated with a lower number of therapeutic agents. Worldwide, it is assumed that only a small fraction of actual cases is reported, thus making it difficult to estimate the true incidence of hepatic disease induced by these substances.

Whereas the use of allopathic drugs associated with self-medication is prevalent in the Brazilian population at large and the wide variety of plants and herbal medicines which is available to the population, it is crucial to know the frequency of drug-induced fulminant hepatitis to prevent risks to the health of the population. Thus, this review aims to ascertain the frequency of drug-induced FHF cases in Brazil and their etiological agents.

METHOD

Literature was reviewed by searching in Medline, LILACS and SciELO databases in January and February 2014. Keywords used were: hepatotoxicity AND Brazil, acute liver failure AND adverse effects, acute liver failure AND drug, fulminant liver failure AND Brazil, acute liver failure AND Brazil, acute liver transplantation AND Brazil, toxic hepatitis, fulminant hepatitis, fatal hepatic failure AND drugs, acute liver failure AND drug reaction, hepatic failure ND herbs, hepatic failure AND medicines, acute liver failure AND herbs, hepatic failure, hepatotoxicity AND Brazil.

Inclusion Criteria: All articles published in English, Portuguese or Spanish with study results, etiology description of FHF cases were included.

Exclusion criteria: Studies in animals or in vitro tests were excluded. Articles that did not show the study's summary and papers that were repeated in more than one database were not included.

Once selected, the full texts were reviewed to determine the relevance of the results to the paper, the number of reported cases, the etiology, age and gender.

RESULTS

In total, 1,556 articles were found in the three databases and analyzed, and one selected article was not indexed in these databases and obtained from the collection of monographs of the Central Library of the Federal University of Bahia, totaling 1,557 publications. Of these, 492 were selected according to inclusion criteria and only 69 dealt with hepatotoxicity studies conducted in Brazil. However, only 15 studies showed results on FHF.

Of the 15 selected Brazilian papers, case studies series were the most frequent (see Figure 1).

Figure 1: Relationship between the type of study and the number of scientific papers found in literature on FHF in Brazil, in the period January-February 2014.

Study design	Number of papers
Case Report	05
Case Series	06
Cross-Sectional	04

According to databases and keywords used in a thirty-year period, 180 FHF cases were published in Brazil. In these results, 20 FHF cases were found, probably associated with DILI (see Figure 2).

Figure 2: Summary of papers in the Brazilian literature on the etiology of FHF

Author	Population	Period	Nº of FHF*	Nº DHP-FHF**
Fonseca J.C.F., *Et al*, 1983[12]	Tropical Medicine Institute of Manaus	Jul-Aug 1983	05 cases	No cases reported
Pires, A.L., *Et al*, 1987 [13]	Clinics Hospital of Porto Alegre	Period is not mentioned	18 cases	No cases reported
Levin, A.S, *Et al*, 1989 [14]	São Paulo Reference Centre	1976-1986	24 cases	01 case
Antoniuk S.A, *Et al*, 1996 [15]	UFP Pediatrics Department	1996	03 cases	03 cases
Beltrame Neto J., *Et al*, 1997 [16]	Clinics Hospital of Porto Alegre	1997	01 case	01 case
Pereira, R.M, *Et al*, 2000 [17]	UNICAMP	2000	01 case	01 case
Moreira-Silva S.F;, *Et al* 2002 [18]	Nossa Senhora da Glória Children's Hospital	1992-1999	46 cases	02 cases
Pacheco- Moreira L.F., *Et al*, 2007 [19]	General Hospital of Bonsucesso-RJ	2001-2006	17 cases	08 cases
Viana C.F. *Et al*, 2008 [20]	Transplant Centre of the State of Ceará	2002 – 2007	20 cases	01 case
Ferreira C. T., *Et al*, 2008 [21]	Clinics Hospital of Porto Alegre	1998-2007	33 cases	No cases reported
Ferraz-Neto *Et al*,2008 [22]	Albert Einstein Hospital-SP	2005-2007	02 cases	No cases reported
Perini, G.F. , *Et al* 2009[23]	Albert Einstein Hospital-SP	2009	01 case	01 case
Cariús L.P., *Et al*, 2009 [24]	General Hospital of Bonsucesso-RJ	2002-2008	07 cases	No cases reported
Santos Júnior, G.O., *Et al*, 2010 [26]	Prof. Edgard Santos University Hospital	2010	01 case	01 case
Bucaretchi F., *Et al*, 2014 [27]	UNICAMP	2013	01 case	01 case

Nº FHF*= number of cases, DHP-FHF**. = Fulminant Hepatic Failure induced by Drugs, Herbal Medicines or Plant Materials

Of the DILI-related FHF cases, it was found that causes associated with the use of allopathic drugs was the most frequent etiology. No food supplement-induced FHF cases have been reported in the literature (Figure 3).

Figure 3. Distribution of FHF cases, per DILI nature, in articles found in the Brazilian literature.

DILI nature*	n	N%
Allopathic Drugs	07	35
Herbal Medicines	0	0
Plant Materials	01	05
Food Supplements	0	0
Nature not identified in the study	12	60

Of the studies that reported DHP-FHF cases, only 6 papers could verify the distribution per gender, and women accounted for 75% (12/16) of cases. Regarding age, in pediatric cases, patients' age range was 4-6 years, whereas adults' age range was 18-47 years.

With regard to drug-related etiology of FHFs described in the literature, it was found that the causative agent is only mentioned in 8 cases, most often cases secondary to the use of valproic acid (see Figure 4). Of the cases described, 60% (12/20) did not identify the etiologic agent, which the article only mentions as "drug-related hepatitis" within FHF frequencies found in the study. The algorithm to validate the adverse reaction was only used in one study.

Figure 4: Distribution of DHP-FHF, per etiologic agent, in papers published in Brazil, during the 1983-2013 period

Etiologic agent	n	N %
Valproic Acid	03	15
Isoniazid	01	05
Paracetamol	01	05
Imatinib	01	05
Plant material	01	05
Halothane	01	05
Number of cases where DHPF was not mentioned*	12	60

*Drug, Herbal Medicine, Plant Material or Food Supplement.

DISCUSSION

Most studies on FHF in Brazil were reports or case series. These are the most common form of publication in journals, although without a high level of evidence, and they are of great relevance to the description of a rare diagnostic entity, especially adverse drug reactions, which for some cases are unusual and require a prolonged exposure for its emergence. Therefore, since FHFs occur in 1:10,000 to 1:200,000 scales, according to international statistics, reports are the most common way of finding this scientific information.

DILIs may seem relatively rare in liver disease; however, they are relatively frequent in reference centers for liver diseases[28].

Drug-induced fulminant hepatic failure accounts for approximately 50% of cases in the United States[29]. According to the results, Brazil seems to have a lower DILI impact than in the U.S., yet national data are scarce.

DILI-related FHF cases account for only 11%, and this result may be due to case underreporting. According to the Pan American Health Organization (PAHO / WHO), underreporting is a common phenomenon worldwide and delays the identification of adverse reaction-related signs and symptoms, leading to underestimation of the size of a health problem. Moreover, this value is higher than what is found in African countries, where drug-induced FHFs account for only 5%[10]. The dearth of African data can probably also explain this phenomenon. Another study conducted in tropical countries involving 430 FHF-affected patients confirms the above results, showing that only 4.5% (19/430) of the cases were attributed to drugs[9].

According to studies found, valproic acid stands out among the drug-related causes of FHF. A WHO study quotes valproate among the five drugs most commonly associated with FHF[30]. However, the fact that valproic acid is the main DILI associated with FHFs must be weighed, since access to and use of this substance for consumption is protected by health regulations, with little association with self-medication.

One of the first papers of literature on the etiology of FHFs demonstrated that 33% (11/33) of cases were associated with drug use, and halothane was identified as the main etiologic agent[31]. Of the cases described in this review on halothane, only 4% (1/24) was associated with this drug. Currently, halothane is rarely used in the country, which justifies the low frequency of cases described in the literature.

Only one case of paracetamol-related FHF was recorded in Brazil. This frequency is lower than that found in countries like the United Kingdom, United States and Scotland[30,32], where high

frequency of this type of FHF is associated with overdose. Another retrospective study, with a sample of 308 patients diagnosed with hepatic failure showed that 39% (120/308) made use of paracetamol, and that, in 83% of cases, a dose higher than 4g/day was used (17 centers)[32]. In Brazilian studies, only one case of probable accidental paracetamol overdose in a child was reported.

Whereas paracetamol is among the most commonly used drugs in self-medication in Brazil, its consumption is significant in the population, so one would expect the emergence of hepatotoxicity cases. However, the few prospective studies in Brazilian literature, coupled with a lack of monitoring on its use do not enable us to certainly affirm the frequency of paracetamol-related hepatotoxicity cases.

Regarding the etiology of herbal medicines and plant materials, only one case secondary to the use of plant material was reported in the Brazilian case studies. In Korea, a retrospective study over a 10-year period demonstrated that 69% (9/13) of FHF cases were secondary to the use of herbal medicines, and of these, 67% (6/9) stemmed from popular-use plant materials[11]. No FHF cases related to the use of herbal medicines were found in Brazilian literature.

Although folk medicine with the use of plant materials and herbal medicine is common in the Brazilian population, this seems not to be a major cause of FHF. Considering that, since 2006, Brazil has a National Policy on Integrative and Complementary Practices within the Unified Health System (SUS) in place, this result reflects underreporting of hepatotoxicity cases caused by these products. Some 77 herbal medicine-related adverse events, or 3% (2/77) of FHF cases, were reported to the National Health Surveillance Agency (ANVISA) over a seven-year period. Health professionals and users alike have trouble in identifying adverse events caused by herbal medicines, due to the lack of a direct correlation of its use with the developed symptom. In England and the US, the underreporting of plant-manufactured drugs is significant, since users do not seek medical advice for their use and do not report their adverse effects (Bames, 2003; Cupp, 1999).

Pediatric-based FHF data shows that, in Brazil, probably three cases were secondary to the use of valproic acid and another case to the use of paracetamol. In a pediatric multicenter study in 24 transplants centers, 19% had FHF secondary to drug use, 14% caused by paracetamol[33]. The same study reveals that, among the most common FHF-related drugs in children are: paracetamol, valproic acid, diphenhydramine, pravastatin, isoflurane, methotrexate, cytoxan, ferrous sulfate, isoniazid (INH), sulfamethoxazole-trimethoprim and minocicline[33].

Imatinib mesylate, a drug used for the treatment of chronic myeloid leukemia, was responsible for a case of FHF. Hepatotoxic reactions of this drug affected 2 to 5% of the patients under treatment[23].

Regarding gender, findings of this study were similar to those reported in other scientific papers, with greater frequency in females[10,11,34,35,36]. As for age, Brazilian studies age range was 18-47 years, whereas the mean age range in most studies found in international literature was ≤ 40 years[10,11,36,37].

Only one of the papers published used algorithms to validate the adverse reaction which was due to the secondary use of a plant material. The algorithms used were RUCAM[38] and Tesckel[39].

Some limitations of this study should be considered: findings were obtained from studies that did not aim to establish the frequency of FHF. In most of the case series published, the drug leading to hepatic damage was not known; the review does not clearly define the number of cases per each etiologic agent and shows the results percentage-wise.

Another aspect that should be considered is the nature of the adverse reaction. Most severe hepatotoxic reactions are dose-dependent reactions which can be prevented.

Most studies do not mention the use of any validation methodology, which compromises the accuracy of the information, making conditional to infer merely a condition of probability for adverse reactions.

CONCLUSION:

FHF cases probably associated with the use of allopathic drugs and plant materials were found in the literature reviewed. Females were the most affected gender, whereas no prevalent age for the onset of hepatic failure could be established, since the disease was distributed heterogeneously.

It was not possible to identify the frequency of FHF in Brazil from the studies found in this review. The scarcity of studies limits the possibility of associating fulminant hepatitis with drug use. More studies are required to better understand the frequency and other potential toxic etiologic agents, as well as the establishment of reaction during case investigation.

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4.2 ARTIGO 2 – FULMINANT HEPATIC FAILURE (FHF) FOLLOWING PROLONGED USE OF HOMEMADE INFUSIONS

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Abstract - 201 words. Main text – 2.257 words.

ABSTRACT

Objective: To describe a case of Fulminant Hepatic Failure after continuous and prolonged use of homemade infusions of "Mãe-boa". **Methodology**: Information was collected at baseline in the pharmaceutical follow-up and from the patient's medical records at the University Hospital Prof. Edgard Santos (HUPES). RUCAM, which ranks its score as "excluded", "unlikely", "possible", "probable" or "highly probable", Naranjo, which ranks its score as "doubtful", "possible", "probable" or "definite" and Teschke et al algorithms were used to assess causality.. **Outcomes and Discussions:** L.S.S, a 23-year old female, was admitted on November 22th, 2007 to the HUPES. She made daily use of herbal supplies popularly known as "Mãe-boa" for two years. The patient's condition worsened. Diagnostic imaging revealed fulminant hepatic failure. Exams results were negative for Anti-HBc, Anti-AgHBs, Anti-HAV (IgM), Anti-HCV, and the anatomopathological test revealed massive hepatic necrosis. According to anatomopathological findings and the exclusion of other causes, liver damage may have been caused by the herbal supply. All the three algorithms used showed some degree of casualty between the use of "Mãe-boa" and the occurrence of FHF. **Conclusion:** The prolonged use of "Mãe-boa" infusions may have caused the development of FHF. Patients should be advice towards the risks of using this plant.

INTRODUCTION

The consumption of botanicals for therapeutic purposes has grown explosively in recent years in western countries[1]. Recent studies show that 42% of Americans use some form of alternative health care treatment, 12.5% make use of plants and, in the last ten years, they account for 20 to 30% of patients with clinical hepatological signs in health care services[2].

In the U.S., it is estimated that approximately 2,000 people per year have Fulminant Hepatic Failure (FHF). Of the reported cases, 13% are idiosyncratic adverse reactions and 10 to 22 / 1,000,000 hospitalizations / year are related to idiopathic hepatitis[3].

A cohort study with a sample of 270 patients showed that 206 (76%) liver transplant recipients were women and 15% of transplants were due to drug-induced hepatic failure[4]. A work performed in tropical countries showed that, of 430 patients diagnosed with FHF, 4.5% were drug-related[5].

Approximately 1% of hepatotoxicity effects are secondary to the use of phytotherapeuticals and herbal supplies[2].Of a series of 20 patients diagnosed with FHF, 35% of cases were due to the use of botanicals.

The mechanism by which phytotherapeuticals cause hepatic damage is unclear. Drugs and chemicals act as direct hepatotoxins or through idiosyncratic inflammatory reactions[6]. A single drug can trigger toxic effects through different mechanisms and thus there is very little knowledge on the pathogenesis of hepatic injury in these cases. Although the toxicity of certain drugs is dose-related, the idiosyncratic drug-induced toxicity suggests important environmental and host-related factors, such as age, alcohol use, gender, preexisting liver disease, kidney disease and genetic factors, such as enzymatic polymorphism. The genetically different isozymes of cytochrome (CYP) P450 may partially explain the observed individual variation in responses to drugs[6].

One of the probable mechanisms can be explained by biotransformation, which generally promotes the modification of a non-polar compound in a polar compound followed by other stages. That is, oxidative pathways mediated by cytochromes (CYP) P-450, resulting in the addition of highly polar groups to the hydroxyl group, but the involvement of glutathione S-transferase, acetylating and alcohol dehydrogenase enzymes[7] can also occur.

The clinical features of hepatic failure are: jaundice, hypoalbuminemia, coagulopathy, disseminated intravenous coagulation, hyperammonaemia, higher serum levels of hepatic enzymes LDH, ALT/SGPT, AST/SGOT, hepatic encephalopathy, hepatorenal syndrome and coma [3,5,8].

Most hepatic injuries include direct hepatocyte necrosis/apoptosis mechanisms and are associated inflammatory with cellular infiltration. Necrosis may be limited to a few scattered cells within the hepatic lobules (focal necrosis), affect certain regions of the lobule (zonal necrosis), entire lobules (submassive necrosis) or the whole liver (massive necrosis). The massive necrosis is also most commonly caused by severe chemical and drug-induced toxicity or viral hepatitis[8].

In folk medicine and more specifically in the State of Bahia, the use of a plant popularly known as “Mãe-boa” is usually assigned to females; it is anti-inflammatory and is used for diseases of the female reproductive organ.

CASE DESCRIPTION

L.S.S, a 23-year old female, 56 kgs, 1.65 m height, Negro, high school student, born in Salvador, Bahia State. She was admitted to the University Hospital Prof. Edgard Santos (HUPES) on 22/11/07 with a moderate pain in the left calf that impaired her walking. The patient developed pain in the abdominal area with fever, sweating, nausea and headache. She reported having had varicella 10 years ago. She has no history of addictions, drank socially on weekends and smoked 1-2 cigarettes at parties. She denied illicit drug use. She reported having seafood allergy.

She used oral contraceptive Ciclo 21® (levonorgestrel 0.15 mg + ethinyl estradiol 0.03 mg) from the laboratory União Química Farmacêutica S/A 4 years ago; 1 tablet per day of Meticorten ® - Mantecorp 5 mg (prednisone) upon seafood consumption. She reported sporadic use of AAS ® - Sanofi-Aventis Farmacêutica Ltda., 500 mg (acetylsalicylic acid) and Anador ® - Boehringer Ingelheim (500 mg) for headaches.

With regard to the use of herbal supplies, she reported making use of homemade infusions popularly known as: Chilean Boldo, *Peumus boldus*, (sporadic use) for abdominal pain, from August to October 2007; capeba, *Piper umbellatum*, 3 times a week, a 200 ml glass of infusion for abdominal pain, from September to October 2007; "Mãe-boa", possibly identified as *Ruellia bahiensis*, from April 2006 to August 2007, daily use of a 300 ml glass. She reported drinking all the infusions at night. L.S.S. reported that botanicals were purchased at a popular fair, namely, the São Joaquim Fair in the city of Salvador, Bahia.

On physical examination, the patient had icteric mucous membranes (++++ / IV), laboratory tests prior to admission with TGO values = 1201 U/L, TGP = 1290 U/L (Chart 1), total bilirubin of 21.71 mg/dL (Chart 2), INR (international normalized ratio) of 2.31 and prothrombin time of 28%. Condition worsened after hospitalization at HUPES. *Abdominal ultrasound imaging* diagnosis revealed acute liver failure , diffuse hepatic echotexture modification and absence of dilated bile ducts.

Chart 01: **Evolution of liver transaminases levels of patient L.S.S. from November to December 2007.**

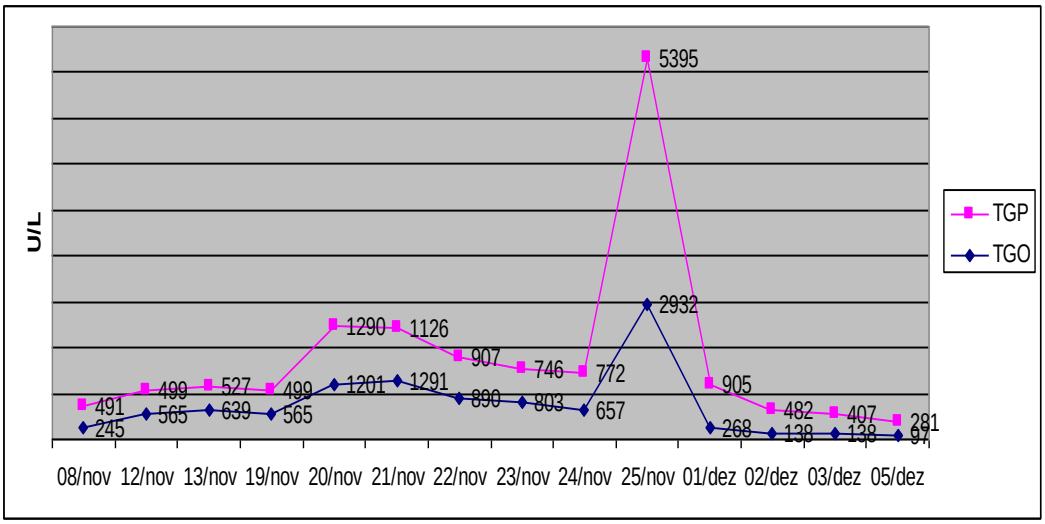
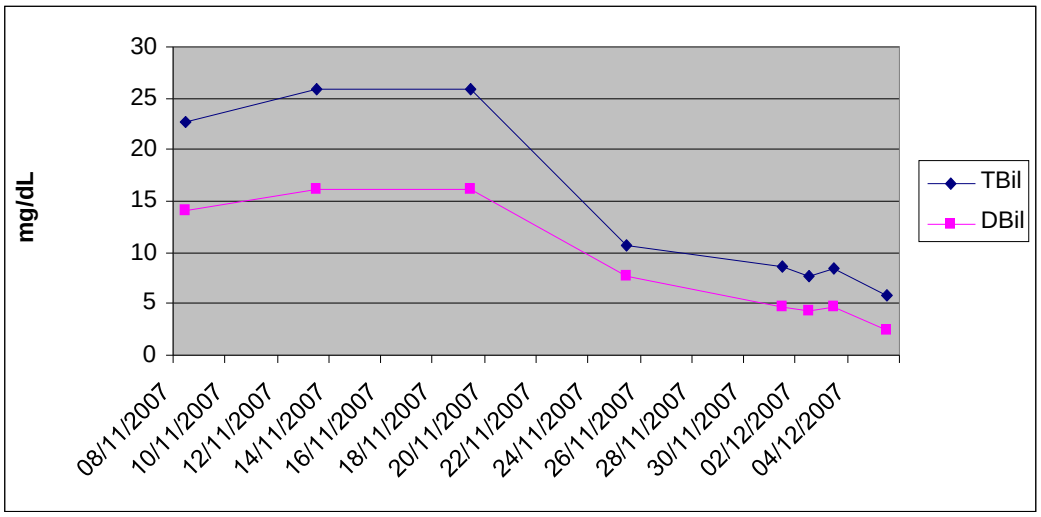


Chart 02: Evolution of Total Bilirubin and direct Bilirubin levels of patient L.S.S. from November to December 2007.



In additional serological tests, the patient tested negative for: Anti-HBc, Anti-HBsAg, Anti-HAV (IgM), Anti-HCV, Toxoplasmosis IgM, Cytomegalovirus IgM, Herpes I and II (IgM), HIV I and II, Anti-nuclear Factor - FAN, Anti-LKM and antimitochondrial antibodies.

On 24/11/07, the patient was transferred to the Beneficência Portuguesa Hospital to undergo liver transplant. The result of the anatomopathological examination revealed extensive hepatic necrosis starting in zone 3, with apoptotic bodies. It found the presence of mononuclear infiltrates with lymphocytes, plasmocytes and xanthomized macrophages. There were no changes in the gallbladder.

Of the drugs mentioned, a drug interaction between the oral contraceptive and prednisone was identified. The first potentiates the adverse effects of the corticosteroid (neurophysiological reactions, electrolyte disorders, hypertension, hyperglycemia), without any relation to liver damage. No interaction between *Ruellia bahiensis* vs. oral contraceptive and *Ruellia bahiensis* vs. prednisone is described in the literature.

With regard to the use of infusions of the other plant species *Piper umbellatum* and *Peumus boldus*, after consulting the database, there are no reports in the literature that associate the use of the earlier plant species and the emergence of hepatotoxicity reactions. However, for the latter, only one case has been reported, namely, that of an elderly patient making concomitant use with laxatives for six months and causing elevation of transaminases.

Firstly, to assess botany, the patient underwent a semi-structured interview on the use of herbal supplies and to identify the botanicals used. The identified species were then collected and forwarded to two university herbaria to be analyzed, and both centers tests were conclusive for *Ruellia bahiensis*.

For the assessment of causality between FHF and possible infusions of *Ruellia bahiensis*, Naranjo algorithm classified it as "possible", RUCAM classified the reaction as "highly probable" and the Teschke et al methodology, which is specific for herbal hepatotoxicity, as "probable".

DISCUSSIONS

This is the first reported and documented case of Fulminant Hepatic Failure caused by the use of possible *Ruellia bahiensis* infusions. According to studies, the use of botanical infusions for therapeutic purposes and the development of adverse reactions secondary to herbal supplies are higher in females (see reference in the original final paper).

Symptoms presented by the patient are clear and typical of fulminant hepatic failure, with jaundice, coagulopathy, hepatic encephalopathy and edema cerebral[11], identified in clinical evaluation, laboratory tests and found further to anatomopathological examination.

Viral etiology tests are essential in these cases, since the prevalence of viral hepatitis in the Brazilian population is 43% for type A (reaching 73% in the Northeast), 1.02% for type B and 1-2% for type C. From what has been shown in the tests collected, these three causes can be excluded since all results tested negative for Anti-HBc, Anti-AgHBs, Anti-HAV (IgM) and Anti-HCV[12].

Autoimmune hepatitis is characterized by the presence of autoantibodies, high levels of serum imunoglobulinemias and frequent association with other autoimmune diseases. It can be characterized by the detection of Anti-LKM (antimicrosomal antibodies) or ANA (antinuclear antibodies)[13]. Following findings in laboratory tests, results were negative for Anti-nuclear Factor - FAN, Anti-LKM, antimitochondrial antibodies. Another variable excluding this etiology is the anatomopathological report, which revealed massive necrosis, presence of apoptotic bodies and massive necrosis in nodules, which characterizes a toxic etiology aggression process.

Other causes of fulminant hepatitis, such as Budd-Chiari syndrome, Wilson's disease and Reye's syndrome were excluded; the patient's clinical evolution and laboratory tests do not characterize any of the aforementioned etiologies[14]. Other disorders that may develop into FHF, such as fatty liver of pregnancy, hyperthermia, hypoxia, malignant infiltration and sepsis[15] were excluded because, following diagnostic and clinical evaluation of the patient, they do not apply to the reported case.

Regarding the use of allopathic drugs, it is estimated that the chemical or drug-induced toxicity is associated with 25%-30% of hepatopathy cases[13]. Among the drugs used by the patient, the oral contraceptive (levonorgestrel + ethinyl estradiol) should be taken into consideration, since the ability to lead to liver damage, especially cholestatic complications[16] is described.

However, according to biopsy results, damage caused by steroids is mischaracterized, as it is histologically defined by cholestasis (dilated canaliculi, brown granules in the cytoplasm of hepatocytes), some level of hepatic cell necrosis, lesions of the biliary ducts lesions and inflammatory polymorphonuclear leukocytes infiltration. Furthermore, the time relationship and use of these drugs, as well as their administration and the time of occurrence of adverse reactions should be analyzed.

From the results obtained after botanical identification of plant species, it is possible that the species responsible for liver damage is *Ruellia bahiensis*. Although the species has been confirmed in two different herbaria, the sample collection following the semi-structured interview was conducted in a popular fair based on the patient’s account.

With regard to the use of other herbal infusions concomitant with infusions of *Ruellia bahiensis*, of the plant species used, just the *Peumus boldus* was reported in the literature of elevation of transaminases following use in combination with laxants for a period of six months[17]. However, when comparing this case, the use of this plant was not daily and the beginning of the administration occurred after the onset of liver toxicity symptoms.

There is nothing conclusive in the literature about the use and toxicity profile of the phytotherapeutic product *Ruellia bahiensis* and its association with the condition developed by the patient. However, the social habits of use of herbal supplies by a female subject can be predictors of the occurrence of the damage, since the idiosyncratic drug-induced toxicity suggests important environmental and host-related factors, such as age, alcohol use, sex, preexisting hepatic disease, kidney disease and genetic factors, such as enzymatic polymorphism[15].

As for the evaluation of causality between the possible use of *Ruellia bahiensis* infusions and FHF, the result obtained by applying the algorithms was classified as possible according to Naranjo[18]. This result can be explained by the fact that some variables of this algorithm, such as the assessment of plasma drug concentration or the use of placebo for the evaluation of the use of herbal supplies are not part of routine health services activities in Brazil.

Another proposal also raised in this algorithm is re-exposure of the patient to the drug. This is not applicable in our case, since the outcome of the reaction does not enable this analysis. These considerations account for the low sensitivity for the assessment of the hepatotoxicity case just by using the Naranjo algorithm. This justifies the use of RUCAM[19], which is more hepatopathy-specific and, more particularly, the algorithm developed by Teschke et al[20] (it provides greater accuracy in the validation of the use of phytotherapeuticals and adverse reactions). For the former, the causality relationship was defined as highly probable, and per the latter, as probable, which sets here a strong association between the use of "Mãe-boa" and FHF.

What should be considered in the Teschke et al algorithm is that one of the proposals of the algorithm questions the existence of Anti-HVE tests. However, even in our case, the fact that this test has not been carried out is not of great importance, since epidemiological data do not suggest a relevant frequency of type-E Hepatitis in the country[13].

FINAL CONSIDERATIONS

Fulminant hepatitis is likely in the patient and is related to the use of *Ruellia bahiensis*, although fulminant hepatic failure secondary to the use of phytotherapeuticals is related to 1% of cases[6]. This small percentage is associated with the absence of pharmacovigilance studies in herbal infusions, phytotherapy, reflecting the lack of research and knowledge about the use of plants and their relationship as an etiological agent for hepatopathy cases.

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4.3 ARTIGO 3 – FULMINANT HEPATIC FAILURE BY MEDICATIONS, ALLOPATHIC, HERBAL , SUPPLIES AND PLANT FOOD SUPPLEMENTS IN REFERENCE CENTRES IN BRAZIL : INTERIM ANALYSIS

SUMMARY

Fulminant hepatitis or fulminant hepatic failure, where loss of hepatocyte function occurs over days or weeks without evidence of cirrhosis, has traditionally been defined by altered mentation accompanied by coagulopathy[1]. It has different etiologies, especially viral hepatitis and drug-induced liver injury (DILI) . According to WHO in a period of 35 years fulminant hepatic failure related to DILI has been reported mainly by the use of drugs, such as paracetamol , flutamina , herbal medicines , herbs and halothane . Although case reports of severe DILI are frequent in many countries, there are few data on the epidemiology of severe DILI in Brazil. **OBJECTIVE**: To determine the frequency of cases of fulminant hepatitis DILI in Brazil. **METHODS**: Retrospective multicenter study. A survey was sent by electronic mail to each center, asking about: operating time of the unit, number of transplants performed, number of fulminant hepatitis and their causes. Subsequently, each center was visited to review the medical files. **RESULTS**: Up to now, of the 60 centers invited, only 05 Liver Transplant Centers (HSC) responded to the survey . From these, 51 cases of Fulminant Hepatitis were evaluated. From these, 33 % (17 /51) were identified as possibly DILI. Non- steroidal Anti-inflammatory drugs (NSAIDs) were the most frequent cause of therapeutic class Fulminant hepatitis. Paracetamol was reported in only one case. Two herbal medicines were identified as the cause of liver injury. **CONCLUSION**: These preliminary data points that DILI epidemiology in Brazil strongly from US and Europe data.

Key words: fulminant hepatic failure, fulminant hepatitis, hepatotoxicity.

INTRODUCTION

Fulminant hepatitis or fulminant hepatic failure, where loss of hepatocyte function occurs over days or weeks without evidence of cirrhosis, has traditionally been defined by altered mentation accompanied by coagulopathy. It is the primary site of xenobiotic metabolism. Facing a toxic injury, the liver may have compromised its function, biliary excretion impairment, inflammatory infiltrate that cause cellular damage and apoptose[1].

Acute severe hepatitis reflects the severe impairment of the liver function [2]. The Clinical features of FH can be evidenced mainly by jaundice, coagulopathy and Hepatic encephalopathy.

The Acute Liver failure or Fulminant Hepatitis (HF) is diagnosed when progressing from symptom onset to hepatic encephalopathy within two to three weeks. This pattern is relatively uncommon and mostly caused by viral hepatitis (50% to 65%) and DILI or chemical substances (25 % to 30 %) [3].

According to WHO in a period of 35 years 4690 cases of DILI were reported to the Center of Uppsala, Sweden. From these, 50 cases progressed to FH. The most common etiologic agents were paracetamol, flutamina, halothane and sulfamethoxazole / trimethoprim. The countries with the highest number of notifications were: United States, United Kingdom and Germany [4] . In parallel, FH caused by herbal remedies, natural medicines and Petrochemicals Plant has been increasingly reported in the literature.

It is estimated that 5-7% of all the transplants in the United States (U.S.) are made by FH. Despite the severity, currently survival rates reaches 46-89 % due to Liver transplantation [5].

In Spain, 461 cases of hepatotoxicity in reference centers, over a period of 10 years, 11.7% of the cases led to liver transplantation or death. Risk factors associated with fulminant hepatitis were female gender, severity of hepatocellular damage and elevated bilirubin[6]. . In Brazil a population of 1622 individuals, 30 % were cases of fulminant hepatitis and 16 % of these were caused by herbal remedies, however it is suspected that these percentages do not represent the epidemiologic reality of this country due to underreporting [7].

According to the latest data from the Brazilian Association of Organ Transplantation (ABTO) , were carried out in Brazil in 2012 , 1,712 transplants in the public health system[8]. Then, the knowledge about the medications and herbs potentially hepatotoxic in our environment can help

prevent cases FH by DILI, as well as reduce the costs of public health liver transplantation. The objective this study is to determine the frequency of cases of fulminant hepatitis DILI in Brazil.

METHODS

Retrospective multicenter study, conducted in Liver Transplant Centers (LTC) in Brazil. Initially, all transplant centers in Brazil, a total of 60 teams, were invited to participate in the study. A formal invitation was sent, by email. Invitations were sent out from September to November/2011

For centers who agreed to participate we emailed an investigation questionnaire that asked about operating time of the unit , number of transplants performed , number of fulminant hepatitis and their etiologies. For those who did not respond during this period, we got in contact by phone call to confirm interest in remaining in the study.

After the Coordinator of Transplant Service having emailed the filled questionnaire, a visit of our team to the LTC scheduled in order to present project , signing of a commitment on participation and declaration of confidentiality. Beyond that, the medical files of index cases were revised. Data collection was performed on revaluation medical records of patients who had the etiology of FH after the use of any allopathic or herbal medicine or food supplement. To collect data from medical records, a previously validated form was used. Socio - demographic information, data on hospital admission, laboratory data, viral serology , autoantibodies , images and , when available , Liver biopsy or pathology of the explant were collected . The entire medication history was carefully revised, taking into account the use of medicines, herbal and dietary supplements. Also, the possibility of drug to drug interactions. When observed associations of medications and / or herbs and/or food supplements were all included in the suspected etiology.

The allopathic medicines to the WHO classification, the Therapeutic Chemical Code (ATC) was used.

The cases that had been previously hospitalized in another Health Unit, we got contact with the respective center to have access to the medical records and complete data collection. .

Inclusion Criteria: All patients admitted in the Transplant Centers who were diagnosed with fulminant hepatitis and transplant indication were included according to the criteria of the

Hospital of King's College (O'Grady et al, 1989)[9]. We suspected FH caused by paracetamol we used the classical criteria: pH <7.3 (regardless encephalopathy) , prothrombin time > 100 seconds creatinine > 3.4 and encephalopathy Grade III / IV . In all other etiologies: prothrombin time > 100 seconds Age < 10 or > 40 years, undetermined etiologies, jaundice - encephalopathy > 7 days, prothrombin time > 50 seconds, bilirubin> 17.5 mg / dL.

Exclusion criteria: cases that lacked information about the drug history prior to admission, the absence of the results of viral serology, autoantibodies and Histopathology were excluded. For cases that were identified an herbal agent , the folowing databases were consulted: MOBOT(Missouri Botanical Garden)[10] , Kew Gardens (Royal Botanic Garders)[11] , Web of Science[12] , Scopus[13] , Medline[14] , Lilacs[15] and SciELO[16] .

This project was approved by the ethics committee of the University Hospital of Bahia-Brazil. For other participating transplant centers, the procedure for submission and approval was conducted. Each Coordinator LTC. presented the approval in their respective Ethics Committees , all necessary project documentation , as recommended by Plataform Brazil system.

For statistical analysis, we used SPSS 18.0 and is used for data analysis descriptive statistics. .

RESULTS

Up to now we visited five from 60 invited LTC. From these, three are located in the Southeast region and two in Northeast. All cases listed were transplants from January 2006 to December 2012. 1,219 liver transplantations were recorded in 06 years of service of the centers (Figure 01) . The uptime of the participating transplant centers ranged from 12 to 22 years. Cases listed for transplantation, 4.5 % (55/1.219) were diagnosed with FH.

Of all patients with FH , four cases were excluded , three because of lack of precise information on medication history and one case of overdose , a drug combination (paracetamol + diclofenac sodium) , counting the end a sample of 51 cases of FH Of these 33 % (17 /51) with probable association with DILI . (Table 01).

All patients transplanted due to FH met the criteria of King's College Hospital . For patients who had DILI, all showed negative serological and autoimmune tests .

Table 01: Etiology of Hepatitis Percussion five LTC, from January 2006 to December 2012.

Etiology	**%**	**n / N**
Drugs	33	17/51
Idiopathic Cause	30	15/51
Autoimmune Hepatitis	13	07/51
Hepatitis B virus	10	05/51
Wilson's Disease	8	04/51
Hepatitis A virus	4	02/51
Hepatitis C virus	2	01/51

Among the patients with probable DILI, 94 % (16/17) were female. The overall mean age was 31.5 ± 13, 5 years and the caucasians prevailed with 76 % (15/17) of cases.

Among the suspected drugs as the cause of FH, 88 % (15/17) had allopathic medicines exposure and 12 % (2 /17) of cases were attributed to the use of herbal remedies. No cases were found associating the dietary supplements with FH in the study sample. By rating A.T.C. 21 % (4 /17) of allopathic medications associated with FH were taken with the aim of treating Musculoskeletal symptoms. (Table 02).

Table 02: Rating A.T.C. allopathic medicines identified as probable etiologic agents of FH in five LTC, from January 2006 to December 2012.

Anatomical group	**%**	**n / N**
Musculoskeletal System	26	4/15
Cardiovascular tract	20	3/15
Nervous System	20	3/15
Genital and urinary tract and sexual hormones	13	2/15
Dermatologicals	7	1/15
Digestive tract and metabolism	7	1/15
General anti-infectives for systemic use	7	1/15

Among the Probable cause FH, 26% (4/17) were secondary to non -steroidal anti- inflammatory drugs (NSAIDs), being represented by the diclofenac sodium and nimesulide. The alphamethyldopa also had an important role. (Table 03).

Table 03: Allopathic Medicines found as probable etiologic agent of fulminant hepatitis in five LTC, from January 2006 to December 2012.

Allopathic drug	**%**	**n / N**
Alfametildopa	19	3/15
Diclofenac sodium	13	2/15
Finasterin	13	2/15
Nimesulide	13	2/15
Amitriptyline	7	1/15
Cimetidine	7	1/15
Fenproporex	7	1/15
Isotretinoin	7	1/15
Macrodantin	7	1/15
Paracetamol	7	1/15

Two herbal remedies used as tee were found in this study: a *Baiensis Ruellia* and *Bidens pilosa* . Both have description at Bank of Mobot and Kew Garden, however, for the first , there are no hepatotoxic reactions reports in the literature, including Medline, Lilacs and SciELO. (Table 04). .

Table 04: Inputs vegetables found as probable etiologic agent of fulminant hepatitis in 05 LTC, from January 2006 to December 2012.

Plant Material	**Popular Name**	**%**	**n / N**
Bidens pilosa	Picão	5	1/17
Ruellia baiensis	Mãe-boa	5	1/17

Regarding risk factors or co-factors, 90% of the cases reported no use of alcohol. No case reported the use of illicit drugs was identified.

The practice of self-medication was found in 47 % (8/17) of the cases. Among the therapeutic indications reported in the medical records by patients for use of drugs or herbal remedies were: arthralgia 24 % (4/17), hypertension 18 % (3/17) and 12 % alopecia (2/17) (Table 05).

Table 05: Description of the therapeutic indications of allopathic medicines or herbal remedies used by patients who have had FH in five LTC, from January 2006 to December 2012. .

Clinical Indication	**%**	**n / N**
Arthralgia	23	4/17
Systemic Arterial Hypertension	17	3/17
Alopecia	12	2/17
Abdominal Pain	6	1/17
Acne	6	1/17
Headaches	6	1/17
Migraine	6	1/17
Not Reported	6	1/17
Urinary Infection	6	1/17
Uterine Inflammation	6	1/17
Weight Loss	6	1/17

Among transplanted patients, the mortality rate reached 77 % (13/17).

DISCUSSION

In five LTC, the number of cases of transplants collected during the study period corresponds only 14 % of the procedures performed in the country. Among the Cases of FH, the DILI appears to be the main cause. Similar results are found in Germany, where 29 % of the FH, are secondary to the use of drugs[17]. However, in USA around 50 % of cases of FH are drugs and paracetamol is the main etiology[18].

In our study, Two cases were associated with the use herbs, as also described by other authors. In a U.S. study 12% of cases of severe DILI were idiosyncratic origin. 11 Most of these reactions occur in 1 per 10,000 to 1 in 200,000 patients, characterized by infrequent occurrence[19] . Diesides that, the intervals between initial exposure and drug reaction action make more difficult to recognize cases of DILI. [39] .This aspects is still more pronounced in case of Herbs, since many other confounding variable could play a role in hepatotoxicity such as: preparation of the herbal remedies, interaction with other herbs or allopathic medicine, time of harvesting the herb, soil that is cultivated to herb. All these variable are almost impossible to be controlled.

The FH attributed to these products in Korea accounts for 69 % (9 /13) of cases[20]. In Hawaii, 29 cases of hepatotoxicity have been reported, with three cases of transplantation due to the use of dietary supplements containing herbs[21] .

The paucity of studies about this topic, and the scarce knowledge about the safety of these products and the fact that most part of the population consider as Herbal medicines innocuous, make the monitoring of these products during their completely neglected. There is still withholding information from the patient, as well as difficulties inherent in diagnosis because of the absence of laboratory markers of DILI. All These factors determine underreporting of cases of hepatotoxicity diagnosis by Herbal Medicines.

In this study, we worked with samples from transplant centers, which may contribute to the low participation of Herbal Medicines in the sample. We know that most of these drugs are toxic events not perceived by the physician or even overlooked by the patient. In addition, most resolved with discontinuation of the drug. Therefore, there are few cases that reach high complexity centers.

It is estimated that herbal remedies are responsible for, at least, 12 % of the causes of FH , but some studies reported up to 67 % (6/9) of cases related this practice .

According to WHO, 65 to 80 % of the world population, in countries like Brazil, still rely on products made from medicinal plants to treat their illnesses[22]. This cultural aspect can not dissociate from the diagnostic investigation of patients with suspected hepatotoxicity. Moreover, it should be understood as underreporting also associated with underdiagnosis phenomenon. In addition, in many parts of the country where herbal medicines are popular, like Amazonia, there is no systematization of drug toxicity , nor easy access to transplant centers.

To make matters worse, some professionals practice what they call *alternative* medicine. Among these not compromised practices, stands out the natural medicine practiced by doctors in Brazil and many other countries. These practices do not usually follow a scientific line, and also stimulate the misconception safety of this treatment. There are many commercial interests that underlie these and other practices, including those that use hormones to counter the physiological aging process, overdoses of vitamins and dietary supplements without evaluation of efficacy and safety. These so-called *alternative* practices tend to overlap, making it even more difficult the diagnosis of hepatotoxicity.

Regarding viral etiologies, the HBV infection was the most common , as observed in two studies , one in Spain and the Republic of Sudan[23]. In Argentina, recent study demonstrated that hepatitis B virus has been responsible for most causes of fulminant hepatitis[24]

On the other hand, Hepatitis A was less frequent than expected in a developing country. The improvements in the HDI in Brazil, has caused rapid change in epidemiology of waterborne diseases in the country. Whereas C virus was the admitted cause of all FH in two cases, we have to be caution before confirming this etiology, since the relation virus v*s* host in Hepatitis C does not offer conditions for developing FH . Thus, an event of hepatocellular aggression otherwise a carrier of HCV can lead to misinterpretation of HCV as the main couse.[25,26].

These preliminary results of our study showed that the FH in Brazil seems to have marked differences compared to other countries.

Probably the reduction of the prevalence of hepatitis B in major cities of the country and the HDI improvements could explain the less important participation of HBV and HAV in FH cases in Brasil [27]. Moreover, Hepatitis B is hyperendemic in the country today in pockets in the Southeast and Northeast, but in rural areas or in small cities with little accessibility to transplant centers included in our sample.

Moreover, this study draws attention to the autoimmune hepatitis (AIH) was the most common non-drug cause of FH Autoimmune hepatitis accounted for 13% of cases. Most international studies do not consider AIH as a major cause of FH[28,29]. Probably many of these cases in our study were diagnosed late, as well as delay in the introduction of immunosuppressors may be responsible for dramatically unfavorable evolution.

The Wilson's disease was the cause of FH in 7% of cases. This finding is similar to what was reported in other countries, such as U.S.A, where the indications for liver transplantation in this etiology is 5 % to 8 % [26].

Despite careful review of medical files, we could not identify the cause of FH in 31% of cases . This finding is supported by most studies, however the number was abnormally higher than that found by other authors, 11 % or 21 %, in Asian countries and in Germany , respectively[20,25] . It is possible that some of these cases may be due to undiagnosed or even not reported use of herbal medications and food supplements. The latter depends on the quality of information passed by the patient or by relatives. It leaves the diagnosis vulnerable to misinterpretations.

Thus, idiopathic causes are considered when there is not enough information about the etiologic agent. Many cases of FH are referred to the health unit and emergency care due to the severity of the disease. Many patients come directly to the transplant , when there is no possibility of collecting detailed information about the use of medications or herbs or food supplements .

In FH Cases caused by DILI, females were more frequent, as described in other studies. The female gender is now considered a risk factor for hepatotoxicity [30,31,32,33,34] . Some authors believe that this finding is due to a confounding factors, because woman usually consume more medications and self-medicate more, thereby increasing the probability of appearance of adverse reactions [35].

The mean age of cases found in this study was lower than reported by other authors[30,31,34,36] . This result may be related to self-medication. The incidence of NSAID -induced liver disease reported in most studies is fairly uniform ranging between 1 and 5 cases per 100,000 persons exposed [4] .The NSAIDs were the most commonly found drug cause, performing 21% of cases . The main agents were nimesulide and diclofenac sodium is touted as one of the 10 drugs most associated with hepatotoxicity[4]. The result of this study corroborates the data on medication use in the Brazilian population, in which NSAIDs are the third most consumed therapeutic class. Other from France and Spain indicate NSAIDs as the second cause of FH by DILI .[36] Recent studies have shown that this toxicity is associated with some polymorphism [37].

The alphamethyldopa was implicated in 20 % of our cases. There are case reports describing the FH after using alphamethyldopa , however actually few studies define the risks for this phenomenon , because this is a largely abandoned drug in many countries[38]. The use of

amitriptyline and macrodantina corresponded to only one case each one. Some reports described the use of these drugs leading to hepatotoxicity [39].

Only 6% of the cases were likely associated with use of acetaminophen in the sample studied. It was much lower than those observed in the USA, Great Britain and Denmark. An American study, conducted from 1998 to 2003 showed that 39 % of fulminant hepatitis causes related to DILI were caused by paracetamol.

In Brazil it is estimated that paracetamol corresponds to 1.4 % of medicines purchased without a prescription in pharmacies[35]. Furthermore, the high frequency FH acetaminophen in Anglo-Saxon countries is related to the use of this drug for suicide, which does not happen in Brazil.

About the indication of the causative drugs of FH In this study, it was found that the arthralgia was the principal. One of the main reasons reported in Brazilian literature that led to self-medication, was the demand for drugs that were related to painful symptoms (headache, muscle pain , cramps , dysmenorrhea)[35]. It means that the basic health care assistance in Brazil needs improvements, specially the Health Family Program.

CONCLUSION

DILI is probably the most common cause of FH in Brazil. The NSAIDs appear to be the main cause of fulminant hepatitis, mainly diclofenac sodium. About 31 % of cases of FH has no definined etiology. Perhaps many of these cases are associated with herbal and/or allopathic medicines and/or food supplements not reported by the patient.

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5 CONCLUSÃO

A insuficiência hepática fulminante na amostra estudada, parece ter como principal etiologia o uso de medicamentos:

- Os Anti-inflamatórios não esteroidais são a classe terapêutica mais frequente como causadora de insuficiência aguda hepática.
- O diclofenaco de sódio é o medicamento mais frequente entre os casos de hepatite fulminante por medicamentos.
- As hepatites autoimunes correspondem à segunda maior causa da amostra, diferente do perfil de outros estudos encontrados na literatura.
- As causas idiopáticas têm uma frequência importante na amostra estudada, o que pode estar associado à baixa informação sobre os casos.
- Os fitoterápicos ou insumos vegetais não parecem ter uma frequência expressiva dentre os casos de hepatite fulminante.
- Não foram encontrados casos associados ao uso de suplementos alimentares nos Centros estudados.
- Faz-se necessária a utilização de algoritmos que possam avaliar a relação causal entre o desfecho e o agente etiológico suspeito nas avaliações dos pacientes com hepatite fulminante nos Centros de Transplante.
- Não se conhece quais são os fatores de risco que podem condicionar o desenvolvimento de IHF por medicamentos na amostra estudada.

6 CONSIDERAÇÕES FINAIS

A avaliação da história medicamentosa é pouco mencionada nos registros do prontuário dos pacientes. Em geral, devido à gravidade do caso, à urgência clínica e cirúrgica, as informações sobre a etiologia não são encontradas, não podendo ser excluídas causas alternativas, como fica definido na metodologia de investigação em farmacovigilância.

Outro aspecto é a utilização de ferramentas para avaliação de causalidade, em nenhum centro pesquisado, houve a menção da utilização de algoritmos ou escalas de avaliação de causalidade.

Este fato também fragiliza os dados já existentes na literatura, sobre as hepatites fulminantes nos estudos, principalmente sobre a etiologia medicamentosa.

Os resultados encontrados neste estudo são um parâmetro para outros trabalhos sobre a frequência da hepatotoxicidade em sua manifestação fatal, bem como pode subsidiar investigações futuras sobre o perfil destas reações adversas.

7. PERSPECTIVAS DE ESTUDOS

A partir dos resultados encontrados, novos estudos podem ser conduzidos, acerca das hepatites fulminantes medicamentosas no Brasil, com os objetivos de:

- Conhecer quais os fatores de risco que podem ser encontrados na população estudada.
- Estabelecer um estudo prospectivo nos centros de transplante, com a utilização de ferramentas de causalidade.
- Conhecer sobre o desfecho de recuperação dos casos de hepatite fulminante medicamentosa.

APÊNDICES

APÊNDICE A – PARECER DO COMITÊ DE ÉTICA E PESQUISA

Parecer Consubstanciado de Projeto

Título do Projeto: Frequência e importância Clínica e Hepatotoxicidade por Alopáticos, Fitoterápicos, Insumos vegetais e Complementos alimentares em Centros de Referência em Hepatologia do Brasil

Pesquisador Responsável Genario Oliveira Santos Junior

Data da Versão 07/06/2011 | **Cadastro** 49/11 | **Data do Parecer** 18/08/2011

Grupo e Área Temática III - Projeto fora das áreas temáticas especiais

Objetivos do Projeto
Conhecer a Frequência de casos de hepatotoxidade causadas pelo uso de alopáticos, fitoterápicos, insumos vegetais e complementos alimentares em centros de referência de alta complexidade em Hepatologia do Brasil.

Sumário do Projeto
Diversos Medicamentos Não Sujeitos a Receita Medica (MNSRM) rotineiramente podem apresentar como efeito adverso significativo à agressão hepática, manifestando-se, em alguns casos, com lesões graves irreversíveis, podendo levar ao óbito.

Estudo multicêntrico retrospectivo no período de 2005 a 2010.

Os dados serão coletados nos diferentes Centros selecionados no Brasil. Serão investigados todos os casos com diagnóstico de hepatotoxicidade no período de 2005 a 2010, conforme critério de inclusão. Será utilizado um formulário para notificação de suspeitas de reação adversa da Agência Nacional de Vigilância Sanitária (ANVISA) para posterior validação.

Para a coleta de dados no prontuário, será utilizada um formulário previamente validado, devendo ser coletado todas as informações relevantes do paciente no que se refere ao internamento na unidade hospitalar e/ou no acompanhamento ambulatorial, além dos dados laboratoriais, diagnóstico de imagem e biópsia necessários para avaliação da casuística.

As suspeitas de reações adversas serão avaliadas para verificar a relação causal entre o uso o medicamento alopático, fitoterápico, insumo vegetal e complementos alimentares e a ocorrência da reação, através da aplicação do Algoritmo de RUCAM e TESCHKE ET AL., instrumentos utilizados para validação de reações hepatotóxicas.

Aspectos relevantes para avaliação	*Situação*
Título	Adequado
Relação dos Pesquisadores	Adequada
Local de Origem na Instituição	Adequado
Projeto elaborado por patrocinador	Não
Local de Realização	Própria instituição
Outras instituições envolvidas	Não
Condições para realização	Adequadas
Introdução	Adequada
Objetivos	Adequados
Método	
Tipo de projeto	Pesquisa em Seres Humanos
Delineamento	Adequado
Tamanho de amostra	Total Na Instituição
Cálculo do tamanho da amostra	Adequado
Participantes pertencentes a grupos especiais	Não
Seleção eqüitativa dos indivíduos participantes	Adequada
Critérios de inclusão e exclusão	Adequados
Relação risco- benefício	Adequada
Uso de placebo	Não utiliza
Período de suspensão de uso de drogas (wash out)	Não utiliza
Monitoramento da segurança e dados	Adequado
Armazenamento de material biológico	Adequado

Instrumentos de coleta de dados	Adequados
Avaliação dos dados	Adequada - quantitativa
Privacidade e confidencialidade	Adequada
Termo de Consentimento	Adequado
Adequação às Normas e Diretrizes	Sim
Cronograma	Adequado
Data de início prevista	
Data de término prevista	
Orçamento	Adequado
Solicita recursos à instituição	Não
Fonte de financiamento externa	Não
Referências Bibliográficas	Adequadas

Recomendação

Aprovar

Comentários Gerais sobre o Projeto

O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 - Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

• O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.

• O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em _____/_____/_____ e ao término do estudo.

Projeto aprovado.

ROBERTO BADARÓ, MD PHD
Coordenador CEP
CHUPES

APÊNDICE B – INQUERITO SITUACIONAL

Sociedade Brasileira de Hepatologia
Av. Brigadeiro Faria Lima 2391 – Conj. 102 – Jd. Paulistano
São Paulo – SP – 01452-000

Nome do Serviço:
Chefe do Serviço:
Contato:
Tempo de Atividade em Transplante (período de observação):

1. Quantos transplantes foram realizados no seu centro ?
2- Quantos destes transplantes foram por Insuficiência Hepática Aguda (IHA) ?
2.1- Quantos casos de IHA foram por drogas?
2.1.1-Destes casos, quantos foram causados por:
Paracetamol
Outros medicamentos alopaticos Qual (is)?
Fitoterápicos Qual (is) ?
Insumos vegetais ? Qual (is) ?
Suplementos alimentares Qual (is) ?
2.1.2 - Voce usou nestes casos algum critério de causalidade ? Qual (is)
2.3.-Quantos destes casos foram de etiologia por vírus A ?
2.4-Quantos destes casos foram por vírus B ?
2.5-Quantos destes casos foram por vírus C ?
2.6-Quantos destes casos foram por outros vírus ?
2.7- Quantos destes casos foram por etiologia indeterminada?
2.8- Quantos destes casos foram por hepatite autoimune
2.9 - Quantos destes casos foram por dç. de Wilson ?
3.0 - Quantos destes casos foram por hepatite isquemica ?
3.1 - Quantos destes casos foram por síndrome de Budd Chiari ?
3.2 - Quantos destes casos foram por afecções hepáticas durante gestação ?
3.2 - Quantos destes casos foram por outras causas ?

APÊNDICE C - FORMULÁRIO DE COLETAS DE DADOS

“Frequência e Importância Clínica da Hepatotoxicidade por Alopáticos, Fitoterápicos, Insumos Vegetais e Complementos Alimentares em Centros de referência em Hepatologia no Brasil.”

FORMULÁRIO

DADOS GERAIS:

1.Ficha n._____

2.Centro:_____

2.1. Serviço: 1. Público 2. Privado 3. Filantrópico

3.Nº PRONTUÁRIO_____

4.Nome**:**_____

5.Idade _____(em anos)

6.Gênero: 1. Masculino 2 . Feminino

7.Peso (kg) :_____Altura (cm)_____

8.Etnia (especificar):1-BRANCO 2-AFRODESCENDENTE 3-ASIÁTICO

10.Cidade/ Estado:_____

HMA:

11. Data da internação:____/____/_____.

12. Quando iniciou o sintomas?_____

13.Qual medicamento, insumo vegetal, complemento alimentar suspeito?_____

_____

14. O uso foi indicação médica ou automedicação? 1.prescrição 2. automedicação

15.Indicação que motivou o uso _____

16. Quando começou o uso? ___/___/___

17. Quando terminou o uso? ___/___/___

18. Qual foi a Posología (mg/h) usada? _____

19. Qual Dose diária (mg) usada? _____

20. Qual o Intervalo (h) _____

21. Qual a vía administração: 1. Oral 2. IV 3. IM 4. SC 5. Sublingual 6. Retal 7. Aerosol 8. Outros _____

ANTECEDENTES PESSOAIS:

22. Possui Comorbidades? 1. Sim 2. Não.

Quais?_____

23. Utiliza medicamentos de uso contínuo? 1. Sim 2. Não
Quais?_____
24. Possui história de uso de álcool? 1. Sim 2. Não
Tipo_____ Quantidade_____
Duração_____
25. Possui historia de uso de drogas ilícitas? 1. Sim Não.
Qual?_____Duração_____
26. Possui história de reações adversas prévias a medicamentos? 1.Sim 2.Não.
Qual?_____

EVOLUÇÃO

27. Paciente foi recuperado? 1. Sim 2. Não
27.1 Data do transplante_____/_____/_____
28. Paciente foi a óbito? 1. Sim 2. Não
29. Data da alta hospitalar_____/____/____
30. Tempo de hospitalização (dias)_____
31.Avaliação de Causalidade RUCAM: ( ) Altamente Provável ( )Provável ( )Possível ( )Improvável.

DADOS BIOQUIMICOS	ANTES TRATAMENTOO	**INICIAL**	**EVOLUÇÃO**	**EVOLUÇÃO**
Glicose (mg/dL)				
Ureia (mg/dL)				
Creatinina (mg/dL)				
Proteínas T (gr/dL)				
Albumina (gr/dL)				
Bilirrubina total (mg/dL)				
Bilirrubina Direta (mg/dL)				
Bilirrubina Indireta (mg/dL)				
AST (UI/L)(VR)				
ALT (UI/L)(VR)				
GGT (UI/L)(VR)				
F.Alcalina (UI/L) (VR)				
Icterícia				
Tempo de Protrombina				
TTPa				
RNI				

MARCADORES	RESULTADO/ DATA	AUTOANTICORPOS	RESULTADO/ DATA
Anti HVA IgM		ANA	
HBsAg		AML	
Anti HBs		AMA	
Anti HBc IgM		Anti LKM-1	
Anti HCV		Anticorpo (SLA, LP)	
PCR HVC			
Anti HEV IgM			
Anti HEV IgM (PCR)			
CMV Ig M			
PCR CMV			
Epstein Barr virus Ig M			
Anti-HIV			

DADOS COMPLEMENTARES

Paciente:_____

1. Quais os sinais e sintomas apresentados?_____

_____
_____
_____

2. Quais alterações foram encontradas no exame físico?_____

_____
_____
_____

3. Antes da internação, o paciente foi atendido em outro local?
Qual?_____

_____
_____

4. Possui resultado de biópsia hepática?_____

4.1.
Laudo/Conclusão:_____

_____
_____