

ETIOLOGY, INCIDENCE AND OUTCOMES OF ACUTE HEPATIC FAILURE IN 0-18 YEAR OLD FILIPINO CHILDREN

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Abstract. Data on the epidemiology of acute hepatic failure (AHF) among pediatric Filipinos is limited. This study investigated the etiology, outcomes and incidence of AHF among 0-18 year old Filipino children. A hospital-based retrospective and prospective surveillance study was conducted at Philippine General Hospital between January 2000 and December 2006. AHF was defined as onset of coagulopathy and/or encephalopathy \leq 28 days after the onset of symptoms, a patient/laboratory prothrombin time $>$ 2, an elevated bilirubin level and evidence of liver failure complicated by encephalopathy. Blood samples were tested for viral hepatitis antibodies using ELISA (Abbott Lab). AHF incidence rates were calculated with 95% confidence intervals (CI). Twenty-seven subjects were recruited and 26 included in the analysis. The mean age of AHF subjects at the time of hospital admission was 6.9 years (SD:6.09 years). The most frequent etiological agents for AHF were hepatitis A virus (HAV) (19.2%; 5/26) and hepatitis B virus (3.8%; 1/26). Incidence of AHF was 11.05 per 100,000 subject years (95% CI 6.81-15.30). Jaundice was observed in 84.6% (22/26) of subjects and encephalopathy on admission (any grade) was reported in 72.0% of subjects. AHF was fatal in 84.6% (22/26) of subjects. HAV was the most common etiological agent for AHF. Indeterminate causes for AHF indicate the need for further investigation.

Keywords: acute hepatic failure, etiology, incidence, outcomes, Filipino children

INTRODUCTION

Acute hepatic/liver failure (AHF/ALF), also known as fulminant hepatic

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failure, is an uncommon clinical syndrome characterized by onset of jaundice, coagulopathy and hepatic encephalopathy within 8-26 weeks of the onset of symptoms of liver disease (Colquhoun *et al*, 2001). It is a condition in which severe liver cell dysfunction leads to multi-organ failure with alteration in the mental status of a previously healthy individual, leading to coma or even death (Ostapowicz and Lee, 2000). AHF, although rare, is

often fatal in children (Kelly, 2002). The recognition of hepatic encephalopathy is difficult in children because the clinical signs are often elusive and appear late in the disease process (Lee *et al*, 2005; Squires Jr *et al*, 2006). This makes the diagnosis of AHF difficult and, unlike in adults, the presence of sensorial changes may not be considered as an essential criterion for diagnosis in children (Durand *et al*, 2001; Baker *et al*, 2004). AHF is a multisystem disease process in pediatric patients with severe liver dysfunction without a previous history of chronic liver disease (Bucuvalas *et al*, 2006).

AHF has a varied etiology worldwide that differs geographically (Takahashi and Shimutzu, 1991; Acharya *et al*, 1996; Lee and Sorrel, 1996). It is difficult to identify AHF in the early stages (Bower *et al*, 2007; Lee *et al*, 2008). The cause of AHF remains unknown in a substantial number of patients (49.0%) despite intensive investigations (Squires Jr *et al*, 2006).

Acute viral hepatitis [hepatitis A virus (HAV) infection] and drug-induced hepatocellular injury are the commonest causes of AHF worldwide. Unlike in adults, HAV infection is usually a subclinical event in children (Schiodt *et al*, 1999) and is often asymptomatic (Gust, 1992). HAV infection has been reported as a common etiological agent in AHF among children (Shah and Habib, 2000; Ciocca *et al*, 2007, 2008). Acute hepatitis B as a cause of AHF is reportedly less common among children than among adults. The underlying etiology is an important factor that determines prognosis and the outcome of AHF. Spontaneous recovery in AHF occurs in 10% to 60% (Alonso *et al*, 2007). Emergency liver transplantation is available option for patients with AHF.

Pre-transplant morbidity and mor-

tality associated with AHF is as high as 74.0% in children (Psacharopoulos *et al*, 1980; Devictor *et al*, 1993), and approximately >80.0% in the adults (Shakil *et al*, 2000; Lee, 2003). Post-transplant mortality rates remain high in children with AHF, with a 6-month survival rate of 76.0% (Baliga *et al*, 2004). No standardized method currently exists for staging the severity of AHF (Liu *et al*, 2006). Orthotopic liver transplantation (OLT) has shown to be beneficial in the treatment of AHF (Lee *et al*, 2008). N-acetylcysteine (NAC), an antioxidant, has been shown to improve outcomes in native livers without transplantation, and survival rates after transplantation (Kortsalioudaki *et al*, 2008).

In the absence of a registry or population-based surveillance programs, the worldwide prevalence of AHF is unclear (Khashab *et al*, 2007). Limited information is available regarding disease burden and etiology of AHF among children worldwide and in Asia. Available published data regarding AHF in the Philippines is also limited. In order to determine the burden of AHF in the Philippines, this study assessed the etiology, outcomes and incidence of AHF retrospectively and prospectively among 0-18 year old Filipino children.

MATERIALS AND METHODS

Study design and participants

This hospital-based study was conducted at the Philippines General Hospital (PGH) between January 2000 and December 2006. PGH is a tertiary state-owned hospital administered and operated by the University of the Philippines Manila, and the University of the Philippines System's Health Sciences Center. It is the largest training hospital in the country designated as the National Uni-

versity Hospital, with a 1,500 bed capacity (1,000 beds for indigent patients and 500 beds for outpatients). It offers some of the lowest rates for patients and on an average, about 600,000 patients visit the hospital each year.

This study was conducted in two phases: retrospective and prospective.

Retrospective phase

Identification of AHF cases among subjects was done through manual review of the hospital discharge log-book using International Classification of Diseases 10 codes and the written diagnosis of AHF. Data were collected from hospital records of eligible 0-18-year-old subjects diagnosed with AHF from January 2000 to February 2006. A workbook was completed by study personnel for each confirmed case to record the diagnosis, etiological viral markers, treatment (liver transplant), outcomes of pathological and physical examination findings.

Prospective phase

AHF was defined as onset of coagulopathy and/or encephalopathy ≤ 4 weeks (28 days) after the onset of symptoms, a prothrombin time > 2 , an increased bilirubin and evidence for liver failure complicated by encephalopathy (Baker *et al*, 2004). Newly diagnosed cases of AHF presenting between February 2006 and December 2006 were identified by the investigator. Medical history and physical examination of newly diagnosed AHF cases were also recorded. Written informed consent was obtained from the subject and parent/guardian prior to enrolment.

The duration of the retrospective component was longer (January 2000-February 2006) than the prospective component (February 2006-December 2006). Due to the rarity of AHF cases, the investigator

combined the two components in order to increase the number of subjects in the study.

The study was conducted according to Good Clinical Practice, the Declaration of Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies (version 1991). The Ethics Committee of the institution approved the study and the study adhered to applicable local guidelines. The study was funded by Glaxo Smith Kline Biologicals.

Data analyses

All analyses were performed on the total cohort of all subjects with AHF who were eligible for the study according to the case definition. Demographic characteristics of subjects (age, gender and race) were tabulated.

The incidence rates of AHF were calculated with 95% confidence intervals (CI) using the population of 0-18-year-olds who live in the Metro Manila area served by the PGH in 2006 as the denominator. The population of 0-18 years was obtained from the Manila Health Center which has a record of the estimated population of Manila stratified according to age.

The incidence of AHF was calculated per 100,000 subject years using the following formula:

Incidence (AHF ≤ 18) =

$$\frac{\text{AHF} \leq 18 \text{ years}}{\text{Population} \leq 18 \text{ years} \times t} * 100,000 * 365.25$$

where:

AHF = the number of AHF cases; Population ≤ 18 years = population of infants and children 0-18 years old who lived in the area of PGH in 2006; t = surveillance period duration (days).

Laboratory assays

Blood samples were collected to detect viral hepatitis antibodies using ELISA (Abbott Lab). Other investigations were

ordered by the attending medical doctor as needed. A urine succinyl acetone test was routinely ordered and metabolic work-ups were requested among patients with suspected metabolic disorders.

Liver function test results [prothrombin consumption time (seconds), peak prothrombin time (seconds), peak total bilirubin test, peak direct bilirubin test, total protein, albumin and liver enzymes [alanine aminotransferase, ALT) and aspartate aminotransferase (AST)] and the outcomes of the AHF cases were recorded. Findings on physical examination, including encephalopathy grade at the time of admission, past medical history of jaundice, liver disease, and history encephalopathy were recorded. During hospitalization encephalopathy grading was also recorded.

All statistical analyses were performed using Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, NC).

RESULTS

Demographic characteristics

Of the 27 subjects enrolled in the study (24 in retrospective phase and 3 in the prospective phase), 26 were eligible for analysis (24 in the retrospective phase and 2 in the prospective phase). One subject (prospective phase) was excluded from analysis due to a protocol violation (the subject's visit date for the study was after completion of the study period). The mean age \pm SD of subjects with AHF was 6.9 ± 6.09 years (range: 0-18 years; median: 6.5 years); 65.4% (17/26) of subjects were males. All subjects were either of East Asian or Southeast Asian.

Etiology

The hepatitis A virus was the most

common identifiable etiological agent for AHF detected in 19.2% (5/26) subjects; Hepatitis B virus was responsible for AHF in 3.8% (1/26) of subjects; in 76.9% (20/26) the etiological agent was undetermined.

Clinical features

Severe encephalopathy (grade 4a or 4b) was reported in 83.3% (15/18) of subjects (Table 1). On admission, jaundice and encephalopathy (any grade) were observed in 84.6% (22/26) and 46.2% (12/26) of subjects, respectively.

Incidence and outcomes

The incidence of AHF was 11.05 per 100,000 subject years (95% CI 6.81-15.30). AHF was fatal in 84.6% (22/26) of subjects. Fifteen point four percent (4/26) of subjects recovered and were discharged from the hospital. No liver transplants were done for any subject during the study.

Laboratory tests

Liver function laboratory results are shown in Table 2. Elevated liver enzymes were seen in 96.2% (25/26) of subjects in the study.

Sixty-five point four percent (17/26) and 80.8% (21/26) of AHF patients were tested for anti-HAV antibodies and hepatitis B surface-antigen. Of these test results, only 29.4% (5/17) of subjects tested positive for anti-HAV IgM and 4.8% (1/21) tested positive for hepatitis B surface-antigen (HBsAg). Acute hepatitis B infection was found in 25.0% (1/4) of subjects, who tested positive for anti-hepatitis B core IgM (Table 3). Only 19.2% (5/26) of subjects were tested for anti-hepatitis C virus, of which one subject (20.0%) tested positive.

DISCUSSION

Similar to other published reports, the present study found the etiology of AHF

Table 1
Severity of encephalopathy in acute hepatic failure cases (total analyzed cohort)
(N = 25).

| Characteristics | Categories | n (%) |
|---------------------------------------|------------|-----------|
| Encephalopathy during hospitalization | Yes | 18 (72.0) |
| | No | 7 (28.0) |
| Grade of encephalopathy | Grade 1 | 0 (-) |
| | Grade 2 | 2 (11.1) |
| | Grade 3 | 1 (5.6) |
| | Grade 4a | 2 (11.1) |
| | Grade 4b | 13 (72.2) |

N, total number of subjects in whom a diagnosis was made; n (%), number (percentage) of subjects in each category

Grade 1 – Child was confused and had mood changes;

Grade 2 – Child was drowsy and displayed inappropriate behavior;

Grade 3 – Child was stuporous but obeyed simple commands;

Grade 4a – Child was comatose but arousable to command;

Grade 4b – Child was in a deep coma and did not respond to any stimuli.

Table 2
Liver function tests (total analyzed cohort) (N = 26).

| Test | Categories | n (%) |
|---------------------------------|------------------|------------|
| Peak prothrombin time (seconds) | Test done | 26 (100.0) |
| | Abnormal results | 26 (100.0) |
| Peak total bilirubin (mg/ml) | Test done | 25 (96.2) |
| | Abnormal results | 23 (92.0) |
| Peak direct bilirubin (mg/ml) | Test done | 25 (96.2) |
| | Abnormal results | 24 (96.0) |
| Peak ALT (IU/l) | Test done | 26 (100.0) |
| | Abnormal results | 25 (96.2) |
| Peak AST (IU/l) | Test done | 26 (100.0) |
| | Abnormal results | 25 (96.2) |

N, number of subjects; n (%), number (percentage) of subjects in each category; ALT, alanine aminotransferase; AST, aspartate aminotransferase

was unknown in the significant majority of subjects (76.9%) (Schiodt and Lee, 2003; Squires Jr *et al*, 2006), despite assessments done in other studies to determine the etiological agents. Among the identified

viral etiological agents in the study, HAV was the most prevalent among Filipino children (19.2%) followed by HBV (3.8%). This mirrors the findings of Schiodt and Lee (2003) who found acute hepatitis A

Table 3
Antibodies against viral hepatitis as measured by ELISA (total analyzed cohort)
(N =26).

| Antibodies | Result | n (%) |
|-----------------------------|-----------------------|-----------------------|
| Anti-HAV IgM | Test done | 17 (65.4) |
| | Positive ^a | 5 (29.4) |
| | Negative ^a | 12 (70.6) |
| Hepatitis B surface antigen | Test done | 21 (80.8) |
| | Positive ^a | 1 (4.8) ^b |
| | Negative ^a | 20 (95.2) |
| Anti-HBc IgM | Test done | 4 (15.4) |
| | Positive ^a | 1 (25.0) ^b |
| | Negative ^a | 3 (75.0) |
| Anti-HCV | Test done | 5 (19.2) |
| | Positive ^a | 1 (20.0) |
| | Negative ^a | 4 (80.0) |

n (%), number (percentage) of children in each category; HAV, hepatitis A virus; HCV, hepatitis C virus; HBc, hepatitis B core

^a Percentages of positive and negative subjects were calculated based on the number of subjects for whom the laboratory test was done.

^b One subject had a positive result on hepatitis B surface antigen and anti hepatitis B-core IgM. Both positive results belonged to the same subject.

and B infections were the most common causes of AHF in children. Furthermore, studies conducted in Asia (Bendre *et al*, 1999; Shah and Habib, 2000), Southern Brazil (Ferreira *et al*, 2008) and Latin America (Ciocca *et al*, 2007) has reported HAV to be a frequent cause of AHF among children (Kelly, 2002). However, HBV as a cause of AHF among adults is more common in Asian countries (Ostapowicz and Lee, 2000).

The outcome with AHF was unfavorable in the majority of children despite improvements in intensive care units, as found in previous reports (Corbally *et al*, 1994; Bhanduri and Mieli-Vargani, 1996; Rivera-Penera *et al*, 1997). This, along with the high mortality rate in our study (84.6%) suggests not just adults are at risk

for fatal outcomes in AHF. A survival rate of 15.4% was observed in our study without liver transplantation. The incidence of AHF among children is mostly unknown (Cochran and Losek, 2007). Reports suggest every year, there are 2,300 to 2,800 AHF cases in the US and 400 cases in the UK (Khashab *et al*, 2007). A study from Scotland (Donnan *et al*, 2007) reported the annual incidence rate of AHF to range from 489 to 869 per 100,000 people. Data regarding incidence rates of AHF from Asian countries is however, limited.

There were a few limitations to this study. Incidence of AHF based on a tertiary hospital setting may be less accurate due to the denominator (hospital catchment) not being well-defined in the study. AHF is a rare disease, therefore, the total

number of subjects enrolled in this study was low; there were no locally available data to enumerate the population aged 0-18 years who lived in the Metro Manila area and attended PGH for treatment. The possibility of patients seeking medical care at other hospitals in the surrounding area cannot be ignored. Some patients at PGH may have come from outside the catchment area. PGH is a tertiary hospital that serves patients who seek medical care from all over the country, so the patients may or may not be from Metro Manila. PGH caters mainly to low-income sectors of the population; those belonging to the middle and high-income sectors would not be included in this study. Therefore, it is difficult to generalize the findings of this study to the overall population of the Philippines.

The viral etiology of AHF was likely underestimated because tests identifying viral agents were not done in all patients. Only seventeen AHF patients were tested for anti-HAV antibodies. The reason for nine subjects not being tested could not be ascertained from the medical records; however, it is assumed these patients might not have the resources to pay for the test because the tests were paid for by the patient themselves and in some patients (neonates), the test might not be indicated. Despite these limitations, these figures on the incidence of AHF in the Philippines present a fair estimate of the relative contribution of different etiological agents and should stimulate further research.

The findings of this study suggested HAV as the main etiological agent for AHF in the Philippines. In some countries (eg Thailand), HAV is not as frequently identified as a cause of AHF and mortality is considerably lower even without liver transplantation. Despite extensive inves-

tigations, the etiology of AHF remained unknown in most cases. Further research to determine the exact etiology and risk factors for AHF is needed to develop potential preventive measures and improved treatment options.

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The authors declare the following conflicts of interest: Fakrudeen Shafi, Yanfang Liu and Salvacion R Gatchalian are employees of GlaxoSmithKline Biologicals, which was the sponsor of this study. Salvacion R Gatchalian owns GlaxoSmithKline stock. Hans L Bock and Irving Boudville were employees of GlaxoSmithKline Biologicals and owns company stock. However, they left the company and no longer own GlaxoSmithKline stocks at the time of manuscript submission. Lulu C Bravo has received consulting fees and honoraria from GSK GlaxoSmithKline Biologicals. Germana V Gregorio declared no conflicts of interest.

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