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Hepatitis E as a Cause of Acute Jaundice Syndrome in Northern Uganda, 2010–2012

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Abstract. Hepatitis E virus (HEV) is a common cause of acute viral hepatitis in developing countries; however, its contribution to acute jaundice syndrome is not well-described. A large outbreak of hepatitis E occurred in northern Uganda from 2007 to 2009. In response to this outbreak, acute jaundice syndrome surveillance was established in 10 district healthcare facilities to determine the proportion of cases attributable to hepatitis E. Of 347 acute jaundice syndrome cases reported, the majority (42%) had hepatitis E followed by hepatitis B (14%), malaria (10%), hepatitis C (5%), and other/unknown (29%). Of hepatitis E cases, 72% occurred in Kaboong district, and 68% of these cases occurred between May and August of 2011. Residence in Kaabong district was independently associated with hepatitis E (adjusted odds ratio = 13; 95% confidence interval = 7–24). The findings from this surveillance show that an outbreak and sporadic transmission of hepatitis E occur in northern Uganda.

INTRODUCTION

Hepatitis E virus (HEV) infection is a major public health problem, causing large outbreaks and sporadic acute hepatitis in developing countries. In 2005, an estimated 20.1 million HEV infections occurred, resulting in 3.4 million acute cases and 56,000 deaths.[1,2] HEV infection is particularly severe during pregnancy; pregnant women are at risk to develop fulminant liver failure and obstetric complications, with a mortality rate as high as 10–25%.[3] During outbreaks, HEV is transmitted by drinking fecally contaminated water, and direct person-to-person contact may contribute to sustained transmission after a common source is removed.[4]

The contribution of hepatitis E to acute viral hepatitis (AVH) is not well-understood. Few studies have shown that hepatitis E is the leading cause of AVH in developing countries.[5,6] However, in many countries, routine etiologic AVH surveillance and laboratory capacity to do so do not exist.[7] Thus, the burden of AVH and the proportion attributable to hepatitis E are not well-known. Owing to the lack of capacity for AVH surveillance, acute jaundice syndrome (AJS) surveillance is used for viral hepatitis in humanitarian emergencies and resource-limited settings.

In recent years, outbreaks of hepatitis E involving several thousand cases have been observed in a number of countries, including countries where it has not been reported in the past.[5] In October of 2007, the largest hepatitis E epidemic among displaced persons in Africa and the first epidemic in Uganda occurred in Kitgum district, northern Uganda.[8] In response to this outbreak, AJS surveillance was established to determine the etiology of AJS and the proportion of cases attributable to hepatitis E and detect outbreaks in neighboring districts of the 2007 outbreak. This report summarizes findings from this surveillance system.

METHODS

Ten healthcare facilities, including Kitgum Health Center located in northern Uganda, participated in AJS surveillance. Healthcare workers in these facilities were trained to identify cases of jaundice. A case of AJS was defined as a person presenting with jaundice of less than 1 month duration and any of the following symptoms: nausea, vomiting, abdominal pain, loss of appetite, fever, itching, joint pain, dark urine, malaise, and headache. A standard form was used to collect data, including age, gender, residence (rural versus urban), disease outcome (including hospitalization and death), and potential risk factors (including drinking water source, treatment of drinking water, handwashing, soap use, latrine use, and contact with a person with jaundice within 2 months before symptom onset). Blood samples were collected by phlebotomy, processed, and shipped to the Uganda Virus Research Institute (UVRI) for hepatitis serology and HEV nucleic acid testing. Blood film was tested for malaria on site.

Laboratory criteria for each type of hepatitis were (1) hepatitis A, immunoglobulin M (IgM) antihepatitis A virus-positive; (2) acute hepatitis B, IgM anti-hepatitis B core antibody (HBc)–positive and hepatitis B surface antigen (HBsAg)-positive; (3) hepatitis C, antihepatitis C virus-positive and IgM antihepatitis A virus-negative, HBsAg-negative, and IgM anti-HEV negative; and (4) hepatitis E, IgM anti-HEV–positive or HEV RNA-positive.

STATISTICAL ANALYSES

Data were entered into the Epi Info database, and analysis was conducted using SAS, version 9.2.[9] Descriptive statistics were used to summarize demographic variables and the proportion of cases attributable to hepatitis E. Logistic regression analysis was used to determine the association between demographics, sanitation and hygiene conditions, and hepatitis E.

RESULTS

From February of 2010 to March of 2012, 347 cases of AJS were reported. The median age of cases was 24 years old

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(range = 1–81 years old), 56% were male, 83% resided in rural areas, 21% were hospitalized, and 2% died. Of 347 AJS cases, 144 (42%) had hepatitis E (Table 1). Of 144 hepatitis E cases, 135 were positive for IgM anti-HEV, 107 of which were also positive for IgG anti-HEV. Of 110 IgM anti-HEV–positive cases that were tested for HEV RNA, 64 (58%) had detectable HEV RNA. Of 122 IgM anti-HEV–negative AJS cases, 9 (7.3%) had detectable HEV RNA by reverse transcription polymerase chain reaction (RT-PCR). The remaining 115 cases were not tested for HEV RNA. Of 144 hepatitis E cases, 44% were female, 86% were in the age group 15–49 years old, 72% were from Kaabong district, 17% were hospitalized, and 1% died. The two deaths in hepatitis E cases were among a 32-year-old non-pregnant female and a 24-year-old male.

Almost all (101 of 104) of the cases from Kaabong were reported in 2011, of which 68% were reported during the months from May to August of 2011 and the remaining 29% occurred during the months from September to December (Figure 1).

Of seven pregnant women with hepatitis E, three women were in the third trimester of their pregnancy, and one woman was hospitalized. Other AJS causes included hepatitis B (14%), hepatitis C (5%), malaria (10%), and other/unknown (29%; includes hepatitis A [2%] and yellow fever [0.7%]) (Table 1). In univariate analyses, age, place of residence, and contact with a jaundiced person were associated with hepatitis E. Residence in Kaabong district was associated with increased odds of hepatitis E (Table 2).

DISCUSSION

AJS surveillance showed that hepatitis E was the most common cause of AJS among patients seeking medical care in northern Uganda. Although hepatitis E infection has been recognized as a major cause of jaundice in developing countries,[10,11] data from this surveillance system clearly showed that a combination of sporadic and outbreak hepatitis E is the leading cause of AJS in northern Uganda. In this study, hepatitis E was independently associated with age and residence in Kaabong district. The temporal clustering of cases from Kaabong represents an outbreak of hepatitis E from May to August of 2011. The characteristics of hepatitis E cases by age group and gender are not different from the commonly observed epidemiologic characteristics of hepatitis E as reported previously.[10,12,13] A high proportion of AJS cases was hospitalized, suggesting that people with severe illness were seeking care at these health facilities.

Unlike reports from India[14,15] and Pakistan,[16] when we exclude cases from Kaboong district (where an outbreak occurred in 2011), we found that hepatitis E is not the most

TABLE 1
Selected demographic and clinical characteristics of patients with AJS by etiology of jaundice in northern Uganda from 2010 to 2012 (N = 347)

	n (%)					
Characteristic	Hepatitis B	Hepatitis C	Hepatitis E	Malaria	Other*/ unknown†	Total‡
Overall	50 (14)	17 (5)	144 (42)	35 (10)	101 (29)	347 (100)‡
Sex						
Female	16 (32)	10 (59)	63 (44)	18 (51)	47 (47)	154 (44)
Male	34 (68)	7 (41)	81 (56)	17 (49)	54 (53)	193 (56)
Age group						
≤ 10	10 (20)	3 (18)	5 (3)	9 (26)	20 (20)	50 (14)
11–20	14 (28)	3 (18)	36 (25)	5 (14)	22 (23)	80 (23)
21–30	13 (26)	3 (18)	60 (42)	14 (40)	31 (32)	121 (35)
31–40	7 (14)	3 (18)	32 (22)	3 (9)	12 (12)	57 (16)
40+	6 (12)	5 (29)	11 (18)	4 (11)	13 (13)	39 (11)
District of healthcare facility						
Abim	4 (8)	3 (18)	10 (6)	16 (46)	23 (22)	56 (16)
Amuru	1 (2)	0 (0)	1 (1)	0 (0)	0 (0)	2 (1)
Dokolo	10 (20)	0 (0)	1 (1)	0 (0)	1 (1)	12 (3)
Gulu	2 (4)	1 (6)	1 (1)	1 (3)	0 (0)	5 (1)
Kaabong	11 (22)	3 (18)	104 (72)	6 (17)	14 (14)	138 (40)
Kitgum	8 (16)	2 (12)	10 (7)	1 (3)	18 (18)	39 (11)
Kotido	10 (20)	5 (29)	13 (9)	7 (20)	36 (36)	71 (20)
Lira	3 (6)	0 (0)	1 (1)	0 (0)	1 (1)	5 (1)
Mbarara	0 (0)	2 (12)	3 (2)	2 (6)	7 (7)	14 (4)
Padler	1 (2)	1 (6)	0 (0)	2 (6)	1 (1)	5 (1)
Place of residence						
Rural	42 (88)	14 (82)	124 (87)	28 (80)	78 (77)	286 (83)
Urban	5 (10)	0 (0)	17 (12)	7 (20)	21 (21)	50 (15)
Camp	1 (2)	2 (12)	2 (1)	0 (0)	0 (0)	5 (1)
Other	0 (0)	1 (6)	1 (1)	0 (0)	1 (1)	3 (1)
Clinical profile						
Inpatient	7 (14)	4 (24)	24 (17)	13 (37)	23 (23)	71 (21)
Outpatient	32 (65)	12 (71)	114 (79)	22 (63)	69 (69)	249 (72)
Unknown	10 (20)	1 (6)	6 (4)	0 (0)	8 (8)	25 (7)
Clinical outcome						
Alive	33 (67)	13 (76)	127 (89)	32 (94)	89 (89)	294 (86)
Dead	1 (2)	1 (6)	2 (1)	1 (3)	1 (1)	6 (2)
Unknown	15 (31)	3 (18)	14 (10)	1 (3)	10 (110)	43 (13)

*Other causes of AJS include hepatitis A (seven cases) and yellow fever (seven cases).
†Unknown causes of AJS (92 cases).
‡Percentages might not add up to 100% because of missing data or rounding.

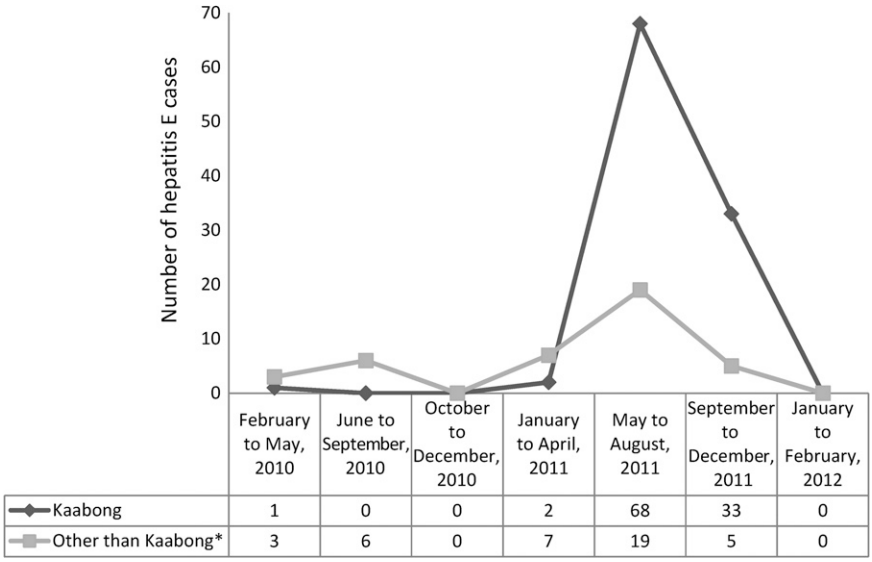

FIGURE 1. Number of hepatitis E cases by months of symptom onset and district in northern Uganda from 2010 to 2012. *Other than Kaabong includes Abim, Amuru, Dokolo, Gulu, Kitgum, Kotido, Lira, Mbarara, and Padler.

common cause of jaundice in sporadic hepatitis cases in the surveillance sites in northern Uganda. The etiologic identification also showed that other hepatitides, including hepatitis B and hepatitis C, were relatively common causes of jaundice. Not surprisingly, hepatitis A was the least common of the causes of AJS.[17]

There are few limitations of our study. The sites were conveniently selected to be contiguous to the outbreak epicenter in northern Uganda. Patients with mild disease without jaundice would not have been detected. Infected infants and young children usually do not have jaundice[18] and therefore, would not be detected by AJS surveillance. Thus, jaundice surveillance might be incomplete but can be a useful index of hepatitis E incidence in an endemic population. We could not ascertain whether antihepatitis C virus-positive cases were currently infected, because we did not have the capacity to

TABLE 2

Univariate and multivariate analyses of factors associated with hepatitis E compared with other causes of AJS in northern Uganda from 2010 to 2012 (N = 144)

Characteristic	Hepatitis E n (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Sex			
Female	63 (44)	Reference	NS
Male	81 (56)	1.05 (0.68–1.61)	
Age group (years)			
≤ 10	5 (4)	0.12 (0.05–0.34)*	0.20 (0.05–0.80)†
11–20	36 (25)	0.83 (0.47–1.47)	0.92 (0.45–1.86)
21–30	60 (42)	Reference	Reference
31–40	32 (22)	1.30 (0.69–2.45)	1.60 (0.73–3.48)
40+	11 (7)	0.40 (0.18–0.87)†	0.45 (0.18–1.13)†
Pregnant			
Yes	7 (15)	0.95 (0.35–2.61)	NS
No	40 (85)	Reference	
District of residence			
Kaabong	104 (72)	12.92 (7.70–21.70)*	13.04 (7.02–24.23)*
Other than Kaabong	40 (28)	Reference	
Source of drinking water			
Safe water‡	114 (88)	Reference	NS
Surface	30 (12)	0.89 (0.53–1.50)	
Boiled and treated			
Yes	29 (21)	Reference	NS
No	111 (79)	0.90 (0.51–1.564)	
Used latrine			
Yes	89 (64)	Reference	NS
No	51 (36)	1.00 (0.63–1.58)	
Contact with jaundiced person			
Yes	54 (39)	1.78 (1.10–2.86)†	NS
No	83 (61)	Reference	
Total	144 (42)		

* $P < 0.0001$.
† $P < 0.05$.
‡Safe water included piped and protected well.
CI = confidence interval; NS = not significant; OR = odds ratio.

determine hepatitis C virus RNA. In some hepatitis B cases, we were unable to determine whether these were acute or chronic infections because of the lack of IgM anti-HBc tests during some of the surveillance period.

Jaundice surveillance is useful in resource-limited settings. If supplemented by etiologic confirmation, this system is effective in identifying cases of hepatitis E, detecting outbreaks, and providing essential data for prevention and control. The lessons learned from AJS surveillance in northern Uganda could be used to improve population-level surveillance and inform comprehensive hepatitis prevention and control strategies and policy, including vaccination.

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