MAJOR ARTICLE

High Mortality Associated with an Outbreak of Hepatitis E among Displaced Persons in Darfur, Sudan

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Background. Hepatitis E virus (HEV) causes acute onset of jaundice and a high case-fatality ratio in pregnant women. We provide a clinical description of hospitalized case patients and assess the specific impact on pregnant women during a large epidemic of HEV infection in a displaced population in Mornay camp (78,800 inhabitants), western Darfur, Sudan.

Methods. We reviewed hospital records. A sample of 20 clinical cases underwent laboratory confirmation. These patients were tested for immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody to HEV (serum) and for amplification of the HEV genome (serum and stool). We performed a cross-sectional survey in the community to determine the attack rate and case-fatality ratio in pregnant women.

Results. Over 6 months, 253 HEV cases were recorded at the hospital, of which 61 (24.1%) were in pregnant women. A total of 72 cases (39.1% of those for whom clinical records were available) had a diagnosis of hepatic encephalopathy. Of the 45 who died (case-fatality ratio, 17.8%), 19 were pregnant women (specific case-fatality ratio, 31.1%). Acute hepatitis E was confirmed in 95% (19/20) of cases sampled; 18 case-patients were positive for IgG (optical density ratio ≥ 3), for IgM (optical density ratio >2), or for both, whereas 1 was negative for IgG and IgM but positive for HEV RNA in serum. The survey identified 220 jaundiced women among the 1133 pregnant women recorded over 3 months (attack rate, 19.4%). A total of 18 deaths were recorded among these jaundiced pregnant women (specific case-fatality ratio, 8.2%).

Conclusions. This large epidemic of HEV infection illustrates the dramatic impact of this disease on pregnant women. Timely interventions and a vaccine are urgently needed to prevent mortality in this special group.

Hepatitis E virus (HEV), a nonenveloped, positive-sense, single-stranded RNA virus, is recognized as the principal cause of enterically transmitted non-A, non-B hepatitis, which occurs worldwide although rarely in industrialized countries [1]. Evidence for the existence of a new epidemiologically distinct virus has been available since the early 1980s, but the virus has only recently been identified [2].

Infections due to hepatitis A virus and HEV are very similar. They are clinically characterized by an icteric phase, with discoloration of sclerae, jaundice, and occasionally dark urine. They are both self-limited, with a low mortality rate in the general population [3, 4]. However, probably the most striking difference between the infections is the high mortality seen among pregnant women with HEV infection, especially those in the third trimester. Case-fatality ratios range from 10% to 42% [5–9].

HEV is transmitted via the fecal-oral route and rarely through person-to-person transmission. HEV is recognized as a common source of waterborne outbreaks, involving fecally contaminated water [3]. The first documented hepatitis E outbreak occurred in Delhi, India, in 1955–1956 [1]. Additional outbreaks have been reported among civilians [10–15] and military popula-

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tions [16–20]. To our knowledge, only 2 episodes have been reported among refugees [4, 21].

In June 2004, a large hepatitis E outbreak occurred in western Darfur, Sudan. A total of 2621 cases were reported between 26 June and 31 December 2004 in Mornay Internally Displaced Persons Camp (78,800 inhabitants). The medical nongovernmental organization Médecins Sans Frontières was the main health care provider in the camp, with a hospital and 2 outpatient departments. The epidemiological investigation suggested an increased risk of HEV infection with drinking water from chlorinated sources [22].

The rationale of this investigation was to collect clinical information on cases of hepatitis E during an outbreak in a large camp, which has rarely been reported. Specifically, we aimed to have a more accurate picture of its impact on pregnant women to provide recommendations for interventions in the future.

METHODS

Description of hospitalized case patients. A clinical case definition was made after the first cases of acute hepatitis E were confirmed on serum specimens at the Naval Medical Research Unit in Cairo, Egypt. Surveillance data in Darfur did not report other diagnoses as important causes of acute jaundice. Therefore, a case of hepatitis E was defined as occurring in a person resident or displaced in Mornay who developed an acute onset of jaundice since 1 July 2004 (defined as a yellow coloration of the sclera). Patients with a positive result of malaria rapid diagnostic test were excluded. Hepatic encephalopathy was classified as either mild (presence of confusion or agitation in addition to jaundice) or severe (presence of coma or convulsions in addition to jaundice). Diagnosis was made by the medical doctor responsible on the ward of admission on the basis of the clinical presentation of patients.

During the presence of the investigation team in the field, a sample of inpatients underwent laboratory confirmation with serological analysis and detection of HEV RNA in serum samples and stool specimens [22]. Acute HEV infection was defined as an optical density (OD) ratio of $\geqslant 3$ for HEV IgG, an OD ratio of >2 for HEV IgM, and/or presence of HEV RNA in stool or serum [22].

Demographic and clinical information was extracted from medical records of hospitalized case patients with hepatitis from 1 July until 31 October 2004. Data were recorded on a standard form; entered into EpiData software, version 3.0 (EpiData Association); and analyzed on EpiInfo software, version 6.04 (Centers for Disease Control and Prevention). The case-fatality ratio among inpatients was calculated using the total number of jaundiced patients admitted at the hospital during the study period as the denominator.

Cross-sectional survey of pregnant women. The study population consisted of all women resident or displaced in Mornay Camp and pregnant between 1 July and 30 September 2004. This included women pregnant at the time of the survey and women who had given birth in the past 3 months. The study population also included pregnant women who had died during the study period. The survey was done by 13 teams of 2 interviewers, 1 team per camp administrative district (limits defined by the camp authorities). Each team was trained to recognize jaundiced persons, and a pilot phase was conducted to ensure compliance with standard procedures and definitions. Data were gathered directly from women or from the nearest relative in case of absence or death of the woman. Information collected included pregnancy status, based on answers given by the interviewee; presence of acute jaundice, defined as yellow coloration of the sclera, either observed by the interviewer or as reported by the interviewee in the study period; and occurrence of death reported by relatives. All pregnant women encountered during the survey were encouraged to seek medical attention even if only mild symptoms had occurred. Attack rates by districts were calculated.

RESULTS

Hospital investigation. The first 2 cases were diagnosed on 7 and 8 July 2004. Both were in pregnant women, who had been admitted to the hospital in coma, who died within 48 h. After this, the number of admitted patients increased each week, peaking during weeks 33–34 and decreasing afterwards (figure 1).

A total of 253 case patients with hepatitis E were admitted to the hospital until December 31. These admissions accounted for 15.3% of all hospital admissions during this period and ranged between 8% of admissions in July (21 of 248) and 27% in August and November (93 of 343 and 26 of 94, respectively).

Twenty serum and 13 stool samples were collected from 20 hospitalized case patients. The diagnosis of acute hepatitis E was confirmed in 19 (95%). Among these 19 with confirmed cases, 18 were positive for IgG (OD ratio, $\geqslant 3$), IgM (OD ratio, >2), or both, and 1 was negative for IgG and IgM but had HEV RNA detected in serum. Among the 18 who tested positive for IgG and IgM, 4 also had HEV RNA present in stool samples, and 3 had HEV RNA present in serum and stool samples.

Demographic and clinical characteristics were obtained from 184 case patients (73%). The majority were adult women (129 [70.1%]), and 143 (77.7%) were aged 15–44 years. Hepatic encephalopathy was recorded in 72 cases (39.1%); it was mild in 35 cases and severe in 37. The median delay before admission was 5 days (range, 1–25 days) (data available for 154 case patients). Duration of hospitalization was available for 180 case patients, accounting for a median duration of stay of 4 days (range, 1–16 days) (table 1). The most frequent symptoms at

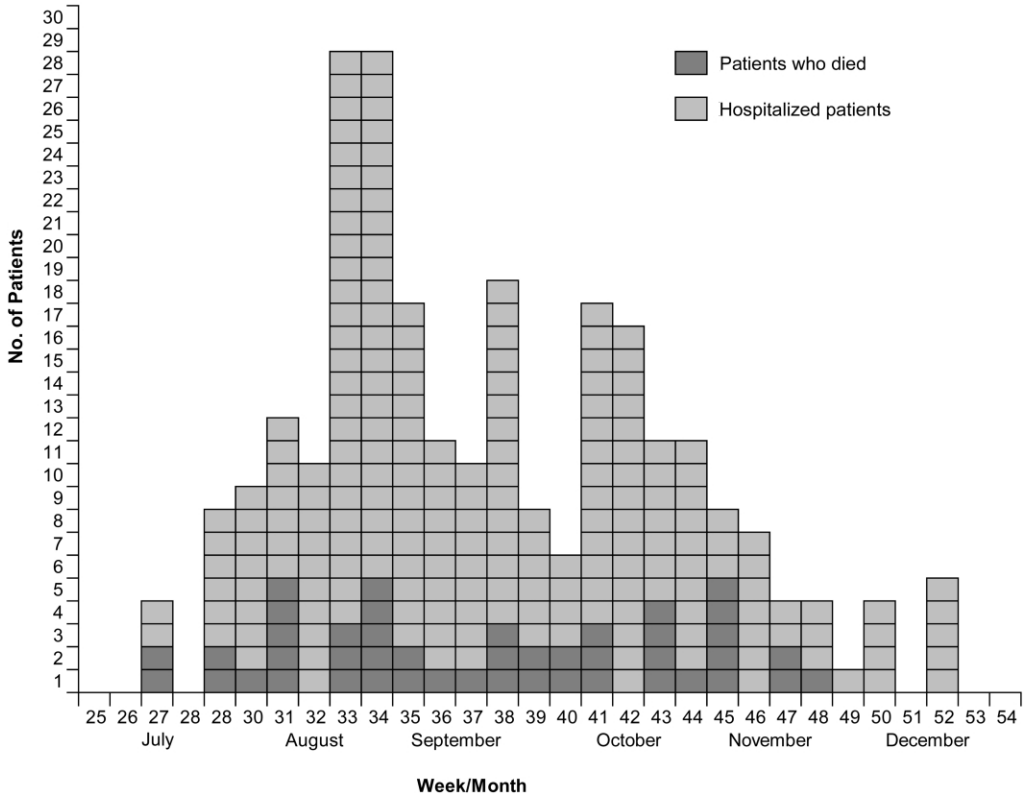

Figure 1. Number of case patients who were hospitalized ($n = 253$) because of jaundice and number who died ($n = 45$), by week of admission to Médecins Sans Frontières Hospital, Mornay Camp, western Darfur, Sudan, July–December 2004.

presentation were jaundice (98%), fever (65%), vomiting (59%), abdominal pain (50%), and anorexia (42%).

Between July and December, 45 case patients with hepatitis E died (case-fatality ratio, 17.8%). Demographic and clinical information were available for 31 of those patients who died: 26 (83.9%) were aged 15–44 years, and 22 (71%) were female. All 31 patients presented with mild or severe hepatic encephalopathy. The median duration of symptoms before admission was 3 days (range, 2–19 days), and the median duration of hospitalization was 2 days (range, 1–7 days) (data available for 26 and 31 cases, respectively) (table 1). Of the 45 case patients who died, 19 (42.2%) were pregnant women, yielding a specific case-fatality ratio in this group of 31.1% (19 of 61 women). The monthly case-fatality ratio for the 6-month period is reported in table 2.

Cross-sectional survey. Overall, 1133 pregnant women were identified during the 2-day survey, representing 1.4% of the Mornay population. Among them, 220 episodes of acute jaundice were recorded during the study period (attack rate, 19.4%). The attack rate among pregnant women ranged between 10.5% ($n = 4$) in Salam 0 district and 33.6% ($n = 41$) in Salam 2 district (table 3). Of 220 pregnant case patients, 18 (8.2%) died (table 3). One-half of the deaths were reported from Shamal 2 district. During the study period, 169 (77%) pregnant women with jaundice had attended a health facility for a medical consultation.

DISCUSSION

To our knowledge, this is the largest outbreak of hepatitis E documented in the literature among internal displaced persons or refugees, illustrating the dramatic impact of this disease on pregnant women at the community level. Between July and December 2004, 2621 cases of hepatitis E were recorded in Mornay camp, accounting for 3% of the camp population [22]. The burden represented by this outbreak is reflected by the proportional morbidity from hepatitis E at the hospital: case patients with hepatitis E occupied, on average, 1 in 7 beds between July and December 2004 and 1 in 4 beds in August at the peak of the outbreak. During that month, on average, 1 patient was admitted each day to the intensive care unit with a diagnosis of hepatic encephalopathy. These figures show the impact of this disease at the hospital level; personnel were overwhelmed with the number of hepatitis E cases and were unable to attend to other patients.

Women represented a large proportion of hospitalized pa-

Table 1. Demographic and clinical characteristics of patients hospitalized with jaundice and case patients who died, Mornay Camp, western Darfur, Sudan, July–October 2004.

Characteristic	All hospitalized case patients	Case patients who died
Age, years		
<5	3 (1.6)	0 (0)
5–14	21 (11.4)	2 (6.5)
15–44	143 (77.7)	26 (83.9)
>45	14 (7.6)	2 (6.5)
Unknown	3 (1.6)	1 (3.2)
Total	184 (100.0)	31 (100.0)
Sex		
Male	54 (29.3)	8 (25.8)
Female	129 (70.1)	22 (71.0)
Unknown	1 (0.5)	1 (3.2)
Total	184 (100.0)	31 (100.0)
Delay before admission, median days (range)	5 (1–25)	3 (2–19)
Duration of hospital admission, median days (range)	4 (1–16)	2 (1–7)
Final diagnosis		
Simple hepatitis	112 (60.9)	0 (0.0)
Mild hepatic encephalopathy	35 (19.0)	9 (29.0)
Severe hepatic encephalopathy	37 (20.1)	22 (71.0)
Total	184 (100.0)	31 (100.0)
Outcome		
Died	31 (16.8)	31 (100.0)
Discharged	149 (81.0)	…
Unknown	4 (2.2)	…
Total	184 (100)	31 (100.0)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

tients, although among patients with hepatitis E, male patients traditionally predominate over female patients at a ratio of 1.5–3.5:1 [23]. Sex distribution might be attributed to a more severe clinical presentation in women, especially those who are pregnant, and/or could reflect the unbalanced sex distribution of the population of Darfur, caused by the violent events occurring since December 2003 and well documented by several surveys [24].

Another unexpected feature of this outbreak was the observed case fatality. Clinical symptoms reported were those typical of hepatitis E, whereas case fatality observed in the hospitalized patients (18%) is higher than reported elsewhere (0%–5.7%) [12, 14, 15, 19, 21]. This result might be explained by the fact that the outbreak at Mornay affected people with impaired health status because of poor living conditions, extremely unsafe sanitary conditions, and poor access to food. Security concerns and lack of confidence in Western medicine might also have delayed seeking access to the healthcare facility. In addition, the extremely difficult working conditions (e.g., lack of proper health care infrastructure and insufficient staff members to ensure an adequate turnover in the hospital), made the treatment and care of these patients particularly difficult and not as effective as it could have been in a more stable setting. All of these aspects may have increased the vulnerability of the population to the severe form of this disease or even worsened the clinical presentation and outcome of patients admitted to hospital.

Almost one-quarter of the patients with hepatitis E admitted to the hospital were pregnant women, and among these, one-third died. In Mornay, the case-fatality ratio among pregnant women admitted to the hospital was almost twice that of other hospitalized patients with HEV infection (42% vs. 18%). This high case-fatality ratio among pregnant women, although still unexplained, is well documented in other studies and was expected in our case series [1, 3, 23, 25].

The cross-sectional survey of pregnant women showed not only a higher case-fatality ratio among pregnant women than among others (31% vs. 18%) but also a higher attack rate than in the camp population (19.4% vs. 3.3%) [22]. However, comparisons must be interpreted with caution, because data were not collected by the same means [22]. In addition, it was not possible to confirm the information gathered, and quality of data is entirely dependent on the respondents' reliability. We could not identify particular risk factors explaining higher attack rates in certain districts than in others. Water supplies in all districts were a mixture of deep-drilled water supply, moderately deep water supply, chlorinated water, and water taken directly from the river.

Whether the higher attack rate and case-fatality ratio among pregnant women are the result of a higher risk of developing symptomatic disease or of an actual increased susceptibility to the infection remains unclear [26, 27]. Some authors suggest that pregnant women are at higher a risk for developing severe acute hepatitis and even fulminant hepatic failure than are the general population, implying that even mild infection during pregnancy might contribute to a rapid progression of infection

Table 2. Monthly case-fatality ratio among overall hospitalized patients ($n = 253$) and pregnant women admitted to hospital ($n = 61$), Mornay Camp, western Darfur, Sudan, July–December 2004.

Month	Proportion of deaths among hospitalized case patients per month (%)[a]	Proportion of deaths among pregnant women admitted to the hospital (%)
July	5/21 (23.8)	4/6 (66.7)
August	15/93 (16.1)	6/15 (40.0)
September	7/47 (14.9)	2/12 (16.7)
October	9/50 (18.0)	1/11 (9.1)
November	8/26 (30.8)	5/10 (50.0)
December	1/16 (6.3)	1/7 (14.3)

[a] These deaths represented, respectively, 5 (14%) of 36, 15 (43%) of 35, 7 (23%) of 30, 9 (38%) of 24, 8 (42%) of 19, and 1 (20%) of 5 total monthly hospital deaths between July and December 2004.

Table 3. Geographic distribution of cases of acute jaundice per camp district, number of deaths, and case-fatality ratio among pregnant women, Mornay Camp, western Darfur, Sudan, July–September 2004.

District	Population	No. of pregnant women	No. of patients with jaundice	No. of deaths	Attack rate, %	Case-fatality rate, %
Salam 0	7383	38	4	1	10.5	25.0
Salam 1	5803	107	16	3	15.0	18.8
Salam 2	7966	122	41	0	33.6	0.0
Salam 3	2558	56	7	0	12.5	0.0
Jebel 1	6822	124	34	1	27.4	2.9
Jebel 2	2886	55	9	0	16.4	0.0
Wadi B	9792	121	14	1	11.6	7.1
Wadi A1	7972	126	18	0	14.3	0.0
Wadi A2	4061	64	18	0	28.1	0.0
Sherig 1	4618	58	7	0	12.1	0.0
Sherig 2	8232	72	13	0	18.1	0.0
Shamal 1	2512	25	3	3	12.0	100.0
Shamal 2	8226	165	36	9	21.8	25.0
Total	78,831	1133	220	18	19.4	8.2

and a higher rate of spontaneous abortion and intrauterine death [10, 28].

Although it was impossible to follow-up these complications associated with HEV infection in hospitalized pregnant women, data in the literature suggest that they may have been severe. In a recent prospective study of 62 pregnant women who had jaundice in the third trimester, HEV accounted for 37% of cases of acute viral hepatitis and 81% of cases of fulminant hepatic failure [29]. More than one-quarter of women with HEV infection had obstetric complications, including premature rupture of membrane, intrauterine growth restriction, placenta previa, and retained placenta. Approximately two-thirds of women with HEV infection had preterm deliveries [29], and in an outbreak in Pakistan, 4 of 8 fatalities occurred among infants born to HEV-infected mothers [10].

Another indirect effect of this outbreak that we did not assess is the number of orphans the outbreak may have caused. Even without quantitative estimates, we can expect this number to be significant because of the high number of children per woman in this setting [24] and the observed high mortality observed among women of childbearing age. Consequences of orphanhood are always severe but can be even more dramatic in an unsafe and unstable context such as western Darfur.

The impact of this outbreak points to the importance of an HEV vaccine as a potential preventive measure. At present, no vaccine is available, although a recombinant vaccine has just undergone clinical trials in Nepal [30]. Some authors have questioned the public health impact of this vaccine compared with improvements in water sanitation and water supply in countries of endemicity [31]. We believe that the prompt use of a vaccine in a context such as Mornay, especially targeting pregnant women, would have dramatically decreased the number of deaths. More research into the development of an effective vaccine is therefore needed. Specific interventions targeting pregnant women concerning water supply, hygiene, and education should also be evaluated. Today, hepatitis E is considered an emerging disease of global importance, but much of our understanding of this disease is still based on outbreak investigations and clinical observations. Aside from the development of a protective vaccine, there is also an urgent need for population-based studies aimed at addressing major epidemiological issues, such as the apparent increased morbidity and mortality in pregnant women, the higher clinical attack rate among adults in outbreaks, the predominance of male patients among clinical case patients, and the importance of animals as a reservoir for HEV. We hope that these studies will prompt detailed investigations of future episodes and possibly their prevention.

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