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Congo/Crimean haemorrhagic fever in Iraq

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Congo/Crimean haemorrhagic fever was recognized for the first time in Iraq in 1979. The first case was reported on 3 September 1979 and since then a further 9 patients have been investigated. Eight patients gave a history of previous contact with sheep or cattle, while 2 patients, a resident doctor and an auxiliary nurse, acquired their infections in hospital by direct contact with patients. The causal virus was isolated from patients' blood and post-mortem liver specimens. The virus isolates were found to be closely related if not identical serologically to members of the Congo/Crimean haemorrhagic fever virus group. Eight of the patients had no epidemiological relationship to one another and lived in widely separated areas around Baghdad and Ramadi (110 km to the west of Baghdad).

Crimean haemorrhagic fever was first recognized in the steppe region of western Crimea, USSR, in 1944. During the summers of 1944 and 1945 over 200 cases of a serious, acute, febrile illness accompanied by severe bleeding occurred and many of the cases were in Soviet troops helping with the harvest (*3*, *4*). Virus strains were isolated from patients' blood and from ticks (*Hyalomma marginatum marginatum*). Later it was realized that a similar disease had been known for many years in the Central Asian Republics of the USSR and the same syndrome has since been described in areas of the USSR bordering the Black Sea and the Caspian Sea, Bulgaria (*10*), and Yugoslavia. In 1970, Casals showed that the Crimean haemorrhagic fever virus strains were antigenically and biologically closely related to Congo fever virus, first isolated in 1956 in Zaire (at that time, Belgian Congo) from the blood of a febrile child (*9*). The virus has since been shown to be widespread in East and West Africa while a related virus, hazara, has been isolated in Pakistan (*1*). Serological evidence suggests that the virus is widespread in Iran (*6*) and there have now been outbreaks in Iraq (*11*, *12*) and the United Arab Emirates (*13*).

This paper describes the clinical and laboratory findings on ten patients infected with Congo/Crimean haemorrhagic fever in Iraq in 1979, the first case having been reported on 3 September 1979.

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CLINICAL FINDINGS

Ten patients were diagnosed clinically as suffering from Congo/Crimean haemorrhagic fever: 8 of the patients were females, 2 were males. Their ages ranged from 18 to 60 years. Eight of the patients lived in widely separated areas around Baghdad and Ramadi (110 km to the west of Baghdad) and had no epidemiological relationship to one another.

The illnesses generally presented with "influenza-like" symptoms of severe headache, fever, backache, anorexia, and vomiting. The principal features are tabulated in Table 1. Several patients suffered from myalgia and arthralgia. Diarrhoea was a prominent feature in 4 patients, while cough, pharyngitis, injected conjunctivae, and pleuritic chest pains were noted in several cases. All the patients developed some form of haemorrhagic tendency between the second and fourteenth days of illness. In most cases bleeding was first noted on the fourth day of illness. Haematomas commonly occurred around venepuncture and injection sites and several patients developed large extravasations of blood on the limbs causing extensive echymotic areas (Fig. 1). Bleeding from the gums, nose, and urogenital tract was commonly seen. In fatal cases severe gastrointestinal bleeding occurred. The three pregnant women all aborted during their illnesses and two of these patients died. Other common features of the disease were jaundice, renal failure, and involvement of the central nervous system in the form of neck stiffness, confusion, and irritability. In fatal cases, the terminal events included irreversible shock, and hepato-renal failure and were

Table 1. Clinical manifestations in 10 patients with Congo/Crimean haemorrhagic fever in Iraq, 1979[a]

Clinical manifestation	No. showing signs
Fever	10
Headache	9
Anorexia	10
Abdominal pain	9
Vomiting	9
Backache	9
Arthralgia and myalgia	7
Diarrhoea	4
Cough	4
Pharyngitis	3
Conjunctival injection	2
Chest pain	2
Bleeding tendency	10
Gastrointestinal bleeding	7
Epistaxis	5
Vaginal bleeding	5
Bleeding gums	4
Abortion	3
Skin haemorrhages	10
Haematuria	9
Hypotension	9
Relative bradycardia	2
Jaundice	10
Palmar erythema	1
Oliguria	8
Hepatomegaly	8
Meningeal irritation	4
Disturbed consciousness	8
Intercurrent infection	8
Death	7

[a] 8 females (3 pregnant) and 2 males.

often exacerbated by intercurrent infection. Pneumonia occurred in 3 cases, *Pseudomonas* septicaemia in 1, and a urinary tract infection in 1 further case.

LABORATORY DATA

The most constant and striking finding was severe thrombocytopenia. Leukopenia associated with the appearance of atypical lymphocytes was common but in some cases leukocytosis was seen in the initial phase of the illness. Mild anaemia was present in all cases from the start of the illness. Erythrocyte sedimentation rates were either normal or slightly elevated. Coagulation studies showed prolonged bleeding times, clotting times, prothrombin times, and partial thromboplastin times (PTT). The serum fibrinogen was estimated in 3 cases and all showed marked

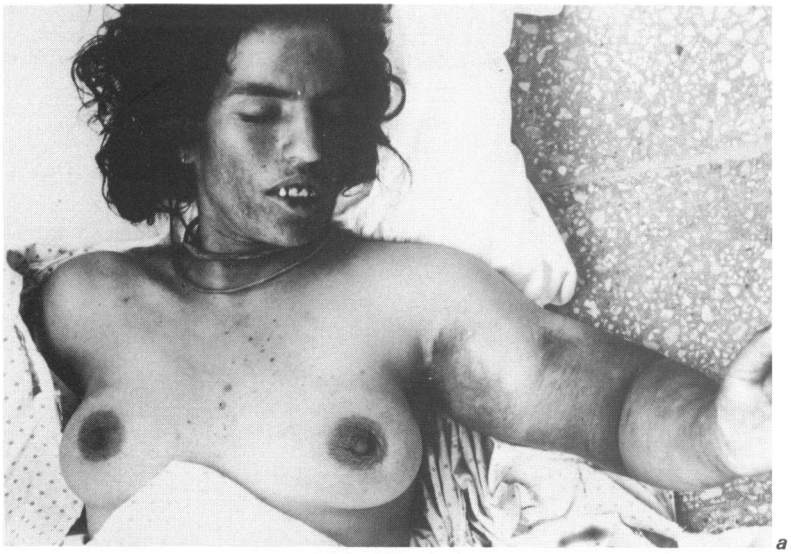
Table 2. Haematological data

Sign	No. of patients/Total
Thrombocytopenia	10/10
Leukopenia	6/10
Atypical lymphocytosis	6/10
Hypocellular marrow	6/10
Prolonged bleeding time	10/10
Prolonged clotting time	4/5
Prolonged prothrombin time	5/7
Prolonged partial thromboplastin time	4/6
Low serum fibrinogen	3/3
High serum fibrinogen degradation products	3/5

depression of fibrinogen levels. The serum fibrinogen degradation products (FDPS) were estimated in 5 cases; 3 had very high levels exceeding 40 g/litre (normal <10 g/litre). The bone marrow was hypocellular in 6 cases; the megakaryocytes were strikingly reduced. Maturation arrest of the myeloid series was also seen in few patients. These findings are summarized in Table 2. Liver function tests were very abnormal, all values being markedly elevated. Serum bilirubin ranged between 65 and 205 μmol/litre (Table 3). Serum iron was found to be elevated in 3 of 4 patients in whom it was estimated. The urine showed albuminuria, granular casts, and microscopic haematuria. Blood urea and serum creatinine levels were elevated, with blood urea around 43.3 mmol/litre and serum creatinine about 1330 μmol/litre in some of the patients.

Table 3. Liver function tests

Sign	Range of levels seen	Normal values
Serum bilirubin	65–205 μmol/litre	20.5 μmol/litre
Serum alanine aminotransferase	54–1385 units/litre	3–36 units/litre
Serum aspartate aminotransferase	88–1638 units/litre	8–33 units/litre
Lactate dehydrogenase	788–2802 units/litre	100–190 units/litre
(L)-lactase dehydrogenase	500–1864 units/litre	0–20 units/litre
γ-glutamyl transferase	53–621 units/litre	5–55 units/litre



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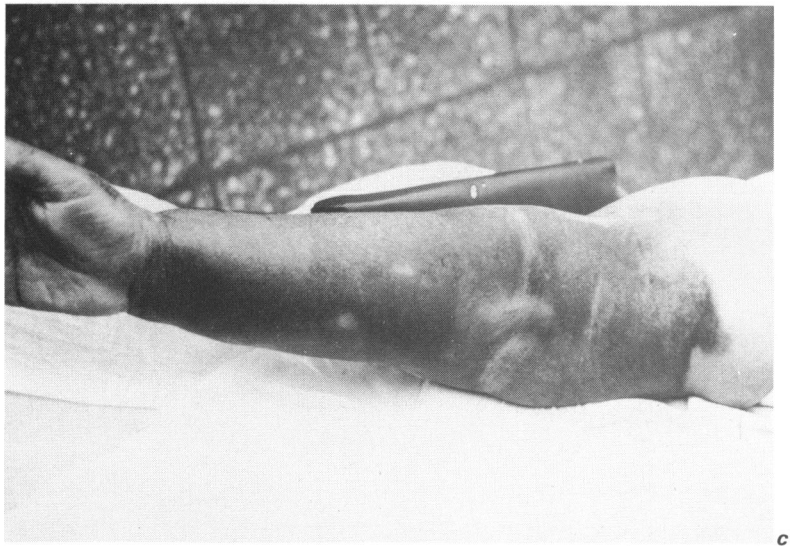

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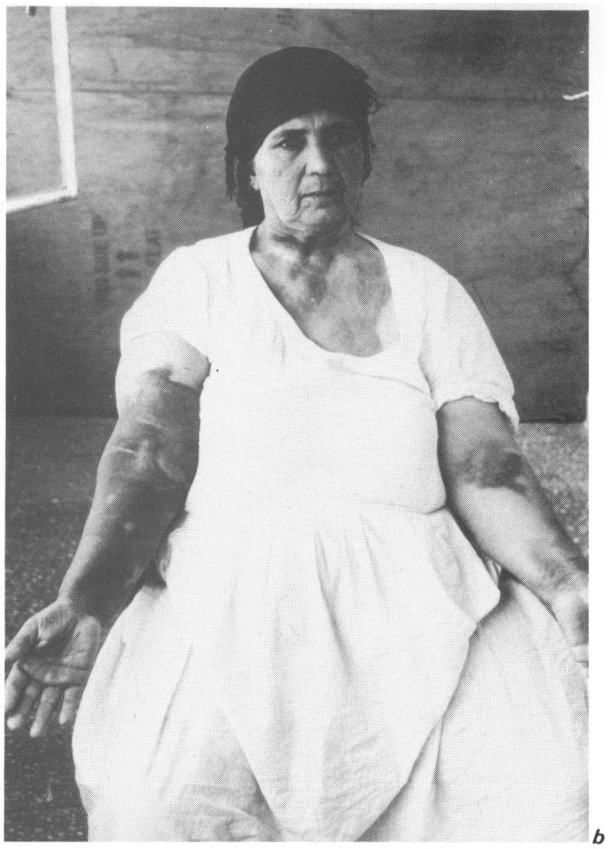

b

Fig. 1. Patients with Congo/Crimean haemorrhagic fever. (*a*) Large echymotic areas on the arm, a purpuric rash on the thorax, and bleeding from the gums. (*b*) Extensive echymoses on the arms and thorax. (*c*) Close-up of the arm of the patient in 1(*b*).

PATHOLOGY

Post-mortem examinations were performed on 2 patients. The organ primarily affected in both cases was the liver, which was slightly enlarged and macroscopically showed yellowish mottling. Extensive liver cell necrosis was seen microscopically, the mid and central zones of the hepatic lobules being most affected. Intracytoplasmic Councilman-like bodies were abundant together with plasma-lymphocytic infiltrates in the necrosed areas of the lobules. The kidneys were also affected in both patients showing a picture of coagulative necrosis affecting the cortical tubules and glomeruli. The central nervous system did not show signs of inflammation or haemorrhage and there was no evidence of direct viral invasion.

VIROLOGICAL METHODS AND FINDINGS

Infectious material

Whole blood was collected during the acute stage of the disease, and liver specimens were collected from post-mortem material from two fatal cases. A 10% homogenate in phosphate buffered saline (PBS) was made from these liver tissues and used for inoculation of cell cultures and animals.

Cell culture

A lamb kidney cell line culture was used for virus isolation. Cells were grown on medium 199 supplemented with 100 g of heat inactivated fetal calf serum per litre and were seeded in 75-cm² plastic tissue culture flasks.

Laboratory animals

Suckling mice, 2–3 days old, were used for virus isolation. The animals were inoculated intracerebrally with 0.03 ml of either blood or liver homogenate.

Antigens

Antigens were extracted from infected mouse brains by the sucrose-acetone method described by Clarke & Casals (*5*). Infected lamb kidney cell cultures underwent 3 cycles of freezing and thawing followed by clarification by centrifugation at 4 °C at 750 *g* for 20 minutes.

Antiserum

Antiserum against Congo fever virus, strain 3010, was supplied by one of us (D.I.H.S.) from the Centre for Applied Microbiology and Research, Porton, England.

Complement-fixation tests

The method of Sever (*7*) was used.

Results of virus isolation

Virus isolations were obtained from the liver and blood of two patients by inoculation of both lamb kidney cell cultures and suckling mice. The virus isolated was later identified by complement-fixation tests and found to be closely related if not identical serologically to members of the Congo/Crimean haemorrhagic fever virus group.

DISCUSSION

During the past few years, sporadic cases of fever with haemorrhagic tendency, but not caused by a primary blood disorder or by a known etiological agent, have been recognized by clinicians in Iraq. They have been ascribed to an unknown viral agent (H. Habib, unpublished data, 1979).

Recently, cases of haemorrhagic fever syndrome have been seen in Iraq and were first reported by WHO (*11*). These were later diagnosed as Congo/Crimean haemorrhagic fever (*12*). During this outbreak, man-to-man transmission occurred in hospital and resulted in the death of 2 hospital staff. A similar mode of transmission was recognized among hospital workers in Pakistan (*8*). Eight of the cases described in this paper had close contact with domestic animals (sheep and cattle). Although no sex predilection has been noted in other countries (*2*), in the present study in Iraq the incidence of the disease among females was high (8 of 10 cases) and might be attributable to the higher exposure risk of females in this country.

The bleeding tendency is attributed to multiple factors including disseminated intravascular coagulation (DIC), bone marrow suppression, and liver dysfunction. One interesting feature of the illness was the shock, which could not be explained solely by the amount of blood lost. Blood replacement did not always correct the hypotension. Other possible causes of shock were examined, including Gram-negative septicaemia, direct vascular damage, and suprarenal haemorrhage, but none of them could be substantiated. Hepato-renal failure was a terminal event in all the fatal cases. Histopathological examination showed that the liver damage was due to direct viral invasion. The renal failure was clinically and pathologically attributed to the hepato-renal syndrome, a known renal complication of advanced liver disease, and to tubular necrosis, secondary to prolonged shock. Neurological manifestations were probably caused by liver and renal failure as no histopatho-

logical evidence of direct viral invasion of the CNS could be demonstrated. Four patients had lumbar punctures and only one had blood in the cerebrospinal fluid.

The relative frequency of intercurrent infections could be explained by the depression of immunity related to the severe leukopenia in some cases, secondary to liver and renal failure and to the administration of massive doses of corticosteroids.

From the therapeutic point of view we feel that supportive therapy in the form of blood and platelet transfusions, rehydration, and aseptic manipulation of patients are more important than corticosteroids and antibiotics. The high mortality recorded in this study is probably due to the inclusion of only severe cases. Patients with minor manifestations were probably missed, being diagnosed clinically as having influenza or enteric fever. The endemicity of the disease in Iraq has not yet been fully studied, but serological surveys are now being organized to seek antibodies against this virus in man and in sheep and cattle from various regions of Iraq.

RÉSUMÉ

FIÈVRE HÉMORRAGIQUE CONGO/CRIMÉE EN IRAQ

Depuis que le premier cas de fièvre hémorragique Congo/Crimée (Congo/Crimean HF) a été signalé en Iraq le 3 septembre 1979, neuf autres malades ont été étudiés. Sur le total des malades, huit (80%) avaient des antécédents de contact avec des moutons ou du gros bétail, alors que deux autres (20%), un interne et une aide soignante, ont contracté l'infection à l'hôpital par contact direct de personne à personne. Le virus causal a été isolé du sang des malades ainsi que du foie à l'autopsie, et des isolements ont également été faits à partir de tiques. On a observé que les virus isolés étaient très semblables mais non identiques sérologiquement aux membres du groupe de virus de la fièvre hémorragique Congo/Crimée.

Pour huit des malades, il n'y avait aucune relation épidémiologique et ils vivaient dans des secteurs éloignés les uns des autres autour de Bagdad et de Ramadi (à 110 km à l'ouest de Bagdad). Il est probable que le virus existait déjà en Iraq depuis un certain temps, mais n'avait pas été identifié auparavant.

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