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Miscellanea.

Hemorrhagic Fever.

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Anmerkung der Redaktion.

Von einem Mitarbeiter in Korea ist der Redaktion der Acta Tropica diese Zusammenfassung über das sog. «Haemorrhagische Fieber» zugegangen. Es handelt sich um eine zuerst in der Mandschurei und in Ostrußland festgestellte Krankheit, die seit 1951 auch in Korea bei den Truppen der Vereinigten Nationen aufgetreten ist. Es wird vermutet, daß es sich um eine Viruskrankheit oder eine Rickettsiose handeln könnte. Da eine direkte Ansteckung von Mensch zu Mensch bisher nie beobachtet wurde, wäre denkbar, daß die Übertragung durch eine Milbe erfolgt; vielleicht figurieren wilde Nager als Reservoirtiere mit inapparenter Infektion.

Definition.

Hemorrhagic fever is considered to be an acute infectious disease, probably of viral or rickettsial origin, characterized by fever, headache, backache and erythematous flush, conjunctival and palatal injection, hemorrhagic manifestations, vaso-motor instability, albuminuria and renal insufficiency.

Etiology.

At present the etiology is unknown. Epidemiologically and clinically, however, hemorrhagic fever behaves like an infectious disease. Attempts by American investigators to isolate an etiologic agent and to transmit the disease to experimental animals have thus far been unsuccessful. On the other hand, Russian and Japanese workers have reported successful transmission to human volunteers by injection of infected blood, urine, and tissue extracts as well as material from infected mites. The Japanese report that the etiologic agent passes a Berkfeld 20 filter, suggesting that it is a virus or small rickettsia.

Epidemiology.

The disease has a seasonal incidence with spring and fall outbreaks. Although sporadic cases occur throughout the year, the case rate rises in May, reaches a peak in June, then declines during the summer months. In October the case rate again rises precipitously and reaches its height in November. During December the case rate falls and cases are infrequent during late winter and early spring.

The Russians and Japanese have reported hemorrhagic fever in Manchuria and Eastern Russia. The 1951 and 1952 outbreaks in United Nations troops have been limited to central Korea, particulary the Chorwon, Kumwha, and Yonchon areas. In Korea, it has been predominantly a disease of front-line troops and its occurs most commonly in personnel whose duties require them to work in grassy and scrub terrain. Small focal outbreaks are seen; thus, for example, three or four cases may occur in one squad while the remainder of the company escapes unaffected. This type of case distribution suggests a non flying insect vector. There is no evidence of person to person transmission.

These observations support the Japanese and Russian claims that the disease is mite-borne. Trombiculid mites are suspected, though no specific

species has been incriminated by American entomologists. At any rate, the bite of the vector does not produce local irritation and there is no eschar.

Foreign literature indicates a reservoir of inapparent infection in field rodents, particularily Podemus aggarius.

Pathology.

The basic pathologic process appears to be diffuse capillary damage with capillary dilation, increased capillary fragility and permeability of the vascular system with transudation of plasma into loose areolar tissues. This leads to hemoconcentration, inadequate circulation blood volume, hypotension, and hemorrhage. Anatomically, the most striking changes are seen in the kidneys and the pituitary. The kidneys are large and edematous. The cut surface presents a striking contrast between the cortex and pyramids. The cortex is pale yellow with petechiae and focal congestion, while the pyramids are dark red and hemorrhagic. Microscopically changes in the cortex are minimal but the pyramidal areas show intense capillary congestion, necrosis of the tubular epithelium and hemorrhage. The anterior lobe of the pituitary shows congestion, necrosis, and hemorrhage, which in 75% of the cases is extreme.

The changes in other organs are less striking. A relatively common finding is hemorrhage into the wall of the right atrium. Epicardial petechiae and subendocardial ecchymoses are found less commonly. The lungs show vascular congestion and, rarely, edema and intrapulmonary hemorrhage. The gastric mucosa is intensely hyperemic and at times hemorrhagic. The adrenals are usually normal but may show lipoid depletion and small hemorrhages. Except for microscopic focal necrosis, the liver is also normal and no consistent changes are found in the brain.

Incubation Period.

The incubation period is usually two to three weeks but may range from seven to thirty-five or more days.

Clinical Picture.

Hemorrhagic fever varies greatly in severity but the majority of the patients follow a relatively typical course. This course, for descriptive purposes, is best divided into four phases. The disease begins with fever and non-specific constitutional symptoms, the febrile phase. In three to five days the temperature falls and at this time many patients show twelve to thirty-six hours of hypotension. This hypotensive phase is followed by three to five days of oliguria and azotemia, and terminates in a diuresis, which initiates the prolonged convalescent phase. The hemorrhagic manifestations begin in the febrile phase, reach their maximum during the hypotensive period and disappear while the patient is still oliguric.

Febrile Phase.

An irregular high fever is characteristic for the first four days of the disease. The usual first symptom is headache, followed rapidly by malaise, anorexia, chilly sensations, and a rising temperature. The headache is severe and usually frontal. Frequently retro-orbital pain, aggravated by ocular movements, is also present. Malaise is especially prominent and is associated with restlessness and weakness, myalgia and lumbar backache. Chill or chilly sensations may be initial symptoms, but more frequently appear four to twelve hours after onset. The temperature rise is rapid and reaches 102° F. or more in the first day in over 90% of the cases. Irregular high fever (101-106° F.) persists

until the onset of hypotension. Lumbar backache is present in twelve to twenty-four hours and becomes progressively worse throughout the febrile phase. Anorexia occurs early and progresses to nausea and vomiting on the third or fourth day of illness, particularly in overhydrated patients, but vomiting is rarely seen in the first forty-eight hours. Thirst is prominent and leads to excessive fluid intake. A few patients notice several soft stools on the first or second day of illness, but the vast majority have no change in bowel habits. Late in the febrile phase, steady, unlocalized abdominal pain appears and may be severe.

Other important but less common symptoms include blurred vision, nasal congestion, and dizziness due to postural hypotension. A mild dry nonproductive cough is common, but not severe.

The two most typical early physical findings are facial flush and injection of the conjunctivae and palate. The flush is diffuse erythema involving the skin of the face, neck, and upper anterior chest and resembles a first-degree sunburn. The injection begins in the palpebral conjunctiva and rapidly spreads to the bulbar areas. It is fine, diffuse, reticulated and not associated with a purulent exudate. The palatal injection is similar and is more prominent posteriorly.

Petechiae are uncommon before the third day. They appear first on the soft palate and in the axillary folds. Subsequently they may occur in the conjunctivae, on the chest, and at the sides of trauma.

Edema of the bulbar conjunctivae and the periorbital tissues may become apparent on the third or fourth day. Diffuse lymphadenopathy begins to appear on the second day. These nodes remain small and non-tender. Splenomegaly and hepatomegaly are rare.

Transient meningismus is seen in a few cases on the second and third day. Costovertebral angle tenderness is not prominent, in spite of the severe backache. Muscle guarding and tenderness to deep palpation may be present in those patients with abdominal pain but rigidity and spasm are not present.

Hypotensive Phase.

Significant clinical shock appears in approximately 25% of hemorrhagic fever patients. With the onset of hypotension the temperature usually falls by rapid lysis. In severe cases the temperature fails to fall, this is considered a poor prognostic sign. Shock is commonest on the fifth or sixth day, but may appear as early as the third. It lasts from a few hours to three days or longer. Significant hypotension is absent in the remaining 75% of the cases and these patients pass directly into the oliguric phase.

Shock is heralded by apprehension, restlessness, and sometimes by diaphoresis. The headache disappears but backache, vomiting and abdominal pain increase. Blurred vision of a myopic type is often prominent. In the more severe patients progressive mental deterioration occurs with confusion, delirium, coma, and occasionally convulsions.

The physical findings in shock are manifestations of wide spread capillary damage. Falling pulse pressure and rising pulse rate characterize the period. The diastolic pressure is maintained initially, thus readings such as 100/80, 90/80, and 86/82 are typical. A thready, weak plus usually persists, but in severe cases blood pressure and peripheral pulse are unobtainable, the neck veins collapse and heard sounds are weak and rapid with an apical rate of 150/min. or more. Cunjunctival edema increases in proportion to the degree of vascular damage. Petechiae appear in increasing numbers, ecchymoses develop at sites of needle puncture and hematemesis may occur. Early the

extremities are dry and warm in spite of hypotension but later cyanosis and vascular stasis appear and the extremities become cold.

In the non-fatal cases these changes regress. The pulse slows, the blood pressure rises and the pulse pressure widens. The edema is slowly reabsorbed and hemorrhagic manifestations lessen.

Oliguric Phase.

Urinary output decreases sharply at the end of the febrile phase and oliguria or occasionally anuria persists for two to six days. The severity of the renal phase is independent of the hypertensive period and severe azotemia may be seen in patients who never show hypotension.

The symptoms of this phase are those of acute azotemia. Often the patients become irritable, restless, and sometimes combative. Vomiting may become a problem. Hiccoughs are common and may become intractable. Neuromuscular hyper-excitability is evident and may progress to tetany. Abdominal pain and backache, on the other hand, regress as the edema is reabsorbed unless the patient is overhydrated.

The blood pressure rises during oliguria, usually to mild hypertensive levels, but it may reach 200/120 and be associated with encephalopathy and convulsions. Bradycardia is common. Uremic frost, pericarditis, diarrhea, and the hyporeflexia and weakness of hyperkalemia may occur in the more severe cases.

Convalescent Phase.

The oliguric phase terminates in a profuse diuresis, usually about the tenth day of illness. In the majority symptoms rapidly subside and convalescence begins. Appetite returns, strength and lost weight are regained. Because of impaired renal concentrating ability polyuria persists. The concentrating ability of the kidneys gradually improves, returning to normal in five to six weeks. This period of time may be as short as two weeks or as long as three months. The severity and duration of the renal involvement determines the length of convalescence.

Laboratory Data.

Albuminuria and hypostenuria are constant findings in hemorrhagic fever. During the febrile phase the urinary specific gravity varies between 1.025 and 1.032. During hypotension and oliguria it falls gradually, reaching 1.010 at the time of diuresis. In the first week of convalescence, specific gravities of 1.004 to 1.008 are common. Concentrating ability, however, returns slowly and is usually the last laboratory test to return to normal. Albuminuria appears suddenly on the third to sixth day and persists until early convalescence. Hematuria may be a manifestation of the hemorrhagic diathesis. It appears microscopically on the third to the fifth day and may progress to gross bleeding during oliguria.

The white blood count is normal in the first three days of illness. Usually on the fourth day the count rises, reaching levels of 20.000 to 30.000 WBC per cu. mm. on the seventh or eighth day. In severe cases counts of 50,000 to 60,000 WBC per cu. mm. are not uncommon and counts up to 100,000 WBC per cu. mm. have been observed. The white blood count then falls slowly, reaching normal levels during the convalescent period. The differential count shifts to the left with the appearance of metamyelocytes and myelocytes before the total count begins to rise. This shift becomes more pronounced until the peak of leucocytosis is reached. On the fourth or fifth day the lymphocyte count rises and many atypical lymphocytes appear. Failure of these cells to

appear is felt to indicate a poor immune response and is a bad prognostic sign. The count returns to normal in convalescence.

The hematocrit is closely correlated to the clinical course of hemorrhagic fever, reflecting diffuse capillary damage and transudation of plasma. It rises slowly during the febrile period. In the hypotensive phase a sudden rise of 10 points or more is usual and levels of 60 or 65 are common. As the blood pressure rises, the hematocrit falls. This decrease of hematocrit continues in the oliguric phase, reaching normal levels before diuresis. As the urine output increases, there may be a mild secondary rise in the hematocrit. A fall to mildly anemic level sometimes appears in convalescence, but this anemia corrects itself without specific therapy. Hemoglobin levels follow hematocrit levels. Occasionally nucleated erythrocytes are seen in the peripheral smear during the acute phase.

The hemorrhagic diathesis is characterized by increased capillary fragility, prolonged bleeding time and thrombocytopenia. Coagulation time and prothrombin levels are usually normal, although clot retraction may be poor. The Rumpel-Leede test becomes positive on the third to fourth day and reverts to normal in the oliguric phase. Platelet depression appears on the fourth day, reaches a maximum on the sixth to seventh day and returns to normal levels during oliguria.

The erythrocyte sedimentation rate is normal throughout the febrile period but rises sharply during oliguria and early convalescence. It falls slowly and reaches normal about at the time of return of normal renal concentrating ability.

Azotemia increases rapidly during oliguria. Because of fever and low caloric intake, catabolism is marked. This leads to liberation of large quantities of nitrogenous wastes, phosphates and potassium. Therefore, blood urea nitrogen levels of 250 mgm.%, phosphate levels of 8-10 mgm.%, and potassium levels of 6-8 mgm./L can appear during a relatively brief period of oliguria. Calcium levels are usually depressed and may reach tetanic levels. Interestingly, acidosis is mild if present, chloride levels are not depressed unless vomiting has been protracted and usually the serum sodium is only slightly depressed. Hyperkalemia, on the other hand, is not uncommon and is associated with characteristic electrocardiographic changes. With the onset of diuresis, creatine levels drop promptly, although the BUN and NPN continues to rise for one or two days. In a minority of cases bizarre electrolyte changes complicate diuresis, but usually chemical abnormalities are promptly corrected. Data on liver function tests, protein fractionation pattern, specific electrocardiographic changes, and steroid excretion are not available.

Diagnosis.

At present there is no specific diagnostic test for hemorrhagic fever. The diagnosis is therefore based on the sum of clinical and laboratory findings. At the Hemorrhagic Fever Center the following criteria are thought to be essential:

1. Clinical history and physical findings consistent with hemorrhagic fever.
2. Hemorrhagic manifestations.
3. Significant albuminuria.

Although milder cases which do not meet these criteria probably occur, they cannot be diagnosed at present.

Diseases most commonly confused with hemorrhagic fever are malaria, upper respiratory infections, infectious mononucleosis, relapsing fever, gastroenteritis, infectious hepatitis, and meningitis.

Complications.

Complications are largely due to the hemorrhagic diathesis. Hematemesis, melena, intrapulmonary hemorrhage, gross hematuria, severe epistaxis, and intracranial hemorrhage may occur, but are rare in patients who are not overhydrated. Bronchopneumonia, pulmonary abscesses, ruptured spleen, hemorrhagic pancreatitis, bacterial parotitis, and cerebral abscess have been encountered.

Prognosis.

The case fatality rate among United Nations troops treated at the Hemorrhagic Fever Center is approximately 5%. Serious prognostic signs are prolonged high fever, early appearance of shock, severe hemorrhagic manifestations, rising temperature during shock, failure of lymphocytosis to appear, marked leucocytosis, and severe electrolyte disturbances. There are no known residues and there have been no proved recurrences.

Treatment.

At present there is no specific therapeutic agent for hemorrhagic fever. Management is based on careful fluid restriction, bed rest, and sedation. Fluid limitation is based on three observations:

1. overhydration increases abdominal pain;
2. mobilization of excessive edema fluid during oliguria when vascular permeability returns to normal may lead to pulmonary edema;
3. excessive edema may aggravate shock. Therefore the presence of conjunctival or periorbital edema, vomiting or severe back pain indicates overhydration and fluid intake is limited. In many patients this produces a moderately negative water balance but improvement in symptoms is prompt and dehydration is well tolerated. On the other hand when overhydration is not a clinical problem fluids may be allowed to the point of equalling urine output plus insensible water loss. When the capillary damage is repaired during oliguria, the edema is reabsorbed and during the remainder of the renal phase the patient is kept in normal fluid balance. With the onset of diuresis negative water balance must be avoided and it is therefore often necessary to force fluids.

It has been amply demonstrated that keeping these patients quiet lessens bleeding, vomiting, shock, and morbidity. Therefore prompt air evacuation, strict bed rest, and adequate sedation are routinely employed. Because it is both analgesic and hypnotic, meperidine hydrochloride has been of great value and is used liberally even when pain is minimal. This drug relieves headache, abdominal pain, vomiting and hiccoughs and produces sleep.

Alcohol sponges, ice packs, and small doses of anti-pyretics are used to control hyperpyrexia, but large doses of acetylsalicylic acid are to be avoided.

Management of the hypotensive phase is directed at maintaining an effective blood pressure without overhydrating the patient until the integrity of the cardiovascular system has been restored. Trendelenburg position and the use of elastic bandages on the lower extremities are effective and these measures alone will control mild to moderately severe cases of shock. Vasoconstrictors are also helpful. Concentrated human serum albumin (salt-poor) is of great value in severe shock, because it increases intravascular osmotic pressure, drawing fluid into the vascular system and reducing hemoconcentration. It loses its effectiveness after repeated use, however, presumably because it leaks into the tissue itself. Human plasma has been used, but this requires large quantities of fluid resulting in increased edema. Whole blood may be effective in reducing shock, its disadvantages are:

1. transfusion reaction;
2. red cell lysis leads to increased danger of hyperkalemia;
3. the fluid volume required would also result in increased edema. Apprehension and hyperventilation during shock are difficult to manage. Constant reassurance and small quantities of sedatives are beneficial.

Therapy during the oliguric phase is essentially that of acute renal insufficiency from any cause. Careful fluid and electrolyte balance is maintained. Intake should be high in calories, in order to reduce endogenous protein catabolism. Diet should be high in carbohydrate and fat, but low in protein sodium and potassium. Hypertonic glycose solutions are useful for these reasons. Large amounts of calcium may be necessary to correct hypercalcemia. Hyperkalemia responds temporarily to hypertonic glucose and insulin, hypertonic saline and calcium. Cation exchange resins and hemodialysis (artificial kidney) have been employed in a few cases.

Except for maintaining adequate fluid and electrolyte intake little therapy is needed after diuresis begins. It is important, however, to keep these patients in bed until azotemia and albuminuria have disappeared. At this time graded ambulation may be initiated. The rate of serious electrolyte disturbances encountered in diuresis must be handled on an individual basis.

Prophylaxis.

Preventive measures are directed at the mite. Dipping clothes after every 2-3 washings in dibutylphthalate and/or benzylbenzoate, use of insect repellent on the boot tops, belt line and hands, and avoiding areas of heavy underbrush whenever possible are thought to be effective in prophylaxis. There is no immunizing agent available at present.