Differential diagnosis of fever syndrome in infectology. Leptospirosis. Haemorrhagic Fevers

V.Bodnar

Aetiology

The causative agents of leptospirosis belong to the family of *Spirochetaceae,* the genus *Leptospira. Leptospira* contains two complexes: *interrogans* and *biflexa.* Each complex has antigenic variations, serovars. Serotypes with common antigens are arranged in serogroups: *Icterohaemorrhagiae, Autumnalis, Canicola, Australis, Pyrogenes, Javanica, Pomona, Ballum, Cynopteri, Celledoni, Semaranga, Andamana.*

Leptospiras survive in moist environment. In water bodies they remain viable for 30 days and more, in soil for 3 months, on foods for several days. Leptospiras withstand low temperatures but are sensitive to high temperature and absence of moisture. Boiling kills them instantaneously.

Epidemiology

The main reservoir of the infection are roddents:
common rats, voles, harvest mice, etc. Another source of infection are leptospirosis cattle, swines, horses, sheep, goats, dogs, and also clinically recovered animals. Human patients are practically safe for the surrounding people. Natural, anthropurgic, and mixed foci of infection are distinguished.
Natural foci of leptospirosis usually occur in the vicinity of rivers, lakes, swamps and moist soils. The infection is transmitted from roddents (which are chronic carriers of the infection) to humans by direct contact and through water or food during agricultural work, fishing, picking mushrooms, drinking water from occasional open sources of water, bathing, walking barefoot, or eating food contaminated with the leptospiras.
Leptospirosis incidence rises in the end of summer and early autumn.

Epidemiology

Cattle, hogs, dogs, and rats are the reservoir of infection in the anthropurgic foci. Poultry and wild birds can also be involved in epizootics. Leptospirosis usually runs a severe course in cattle, especially in calves. In swines, leptospirosis is usually characterized by mild clinical symptoms. The animals shed leptospiras in their urine. Leptospira carrier state can persist from a month to a year and longer.

The main factor transmitting the infection from the diseased animals to man is water. Humans (especially persons with an empty stomach) get infected by drinking contaminated water, or when bathing in an open water body infected with the animal excrements. Leptospira penetrates through the mucosa of the mouth, eyes, nose, and through abraded skin during bathing, when working barefoot on rice plantation, etc.

Epidemiology

Less frequently man is infected by drinking milk of diseased animals or by ingesting food contaminated with the infected urine. Man is also infected by contact with the infected objects, when taking care of diseased animals, during slaughtering diseased animals, and processing their tissues. Common brown rats are the source of infection in large cities, especially in sea ports. Deratizators and sanitary workers are especially exposed to the danger of infection. Outbreaks and sporadic infection cases are possible among stevedores and miners.

In anthropurgic foci, leptospirosis occurs during the whole year in the form of sporadic cases.

Pathogenesis

Motility of leptospiras helps them overcome the defense barriers and enter the blood circulating system. Blood carries them to various organs, mainly to the liver, kidneys, spleen, lungs, etc. This process is actually the incubation period.

The onset of the disease is characterized by re-entry of the decayed leptospira and their metabolites into the blood which carries them to various organs and tissues, especially to the kidneys, the adrenal glands, the liver, and the meninges. Beginning with the second week of the disease, in connection with marked toxaemia, the capillaries are damaged, their permeability increases to cause the haemorrhagic syndrome (bleeding into the internal organs and the skin).

Lesion of the liver cells and, to a lesser degree, red cell haemolysis due to the effect of leptospiral haemolysins, evoke jaundice. Complications in the kidneys, the nervous system and the eyes can develop during this period. Leptospiras are liberated into the environment with urine for several weeks. They can be detected also in the liquor. Recovery begins with the production of immunity to the specific serotype.

Clinical picture

The incubation period varies from 6 to 20 days
(usually from 7 to 12 days).
Anicteric and icteric forms of leptospirosis are differentiated.
The onset of the disease is sudden and acute.
The patient complains of chill, his temperature quickly rises to 38-40 °C. The common symptoms are weakness, lassitude, persistent headache, insomnia, myalgia (especially in the calves and the neck). The face is hyperaemic, the scleral vessels injected, with haemorrhage into the sclera, the tongue is coated and dry. Scarlatina-like and measles-like rash develops in 4-5 days. Roseolas and petechiae are less frequent (usually in severe cases). Rash appears instantaneously on the chest, abdomen and the limbs. The liver is enlarged and tender to palpation. Some patients develop the haemorrhagic syndrome at the beginning of the second week: petechiae on the skin, ecchymosis at the sites of injection, nasal, gastric, intestinal, and uterine haemorrhages, blood spitting, haemorrhage in the brain, myocardium and other organs. The platelet count is low.

Clinical picture

Symptoms of nephritis can develop. In mild cases, the urine of patients contains small amounts of protein, single red cells, white cells, and hyaline casts. In anicteric cases, jaundice is either absent or mild. Severe disease is characterized by high body temperature that persists for 6-10 days. In the icteric form of the disease, the sclera and then the skin turn yellow in 3-5 days of the disease. The urine is also dark. The conjugated bilirubin of blood is high. After jaundice develops, the body temperature decreases critically or by an accelerated lysis. The patient's condition improves. Oliguria develops from the very first days of the disease, and becomes especially marked in 7-10 days. The protein level in the urine is high; the quantity of red and white cells, of hyaline and granular casts is also increased. Rest nitrogen of blood increases too.

Clinical picture

If the disease runs a benign course and treatment begins in due time, oliguria is superseded by polyuria in the end of the second week; the pathological changes in the urine gradually subside. If the course of the disease is unfavourable, death is possible due to renal failure and uraemia.

Haematologic changes include hypochromic anaemia, low haemoglobin (to 64-80 g/l), thrombocytopenia, leucocytosis (10-12 x 10^9/l), neutrophilosis with a shift to the left, aneosinophilia, and lymphopenia; ESR accelerates to 50-60 mm/h. In 5-6 days after normalization of body temperature, some patients develop an exacerbation.

Fever during the relapse lasts from 3 to 9 days.

Complications

Severe leptospirosis can be complicated by renal failure, acute hepatorenal failure, acute cardiovascular failure, haemorrhage, myocarditis, meningitis, encephalitis, pneumonia, otitis, and diseases of the eye.

Diagnosis

The diagnosis is based on clinical and epidemiologic findings.

It is necessary to examine blood taken from the ulnar vein during the first 4-5 days of the disease; 2 ml should be used for microscopy, and 4 ml for cultivating a blood culture on a water-serum medium (distilled water and rabbit serum). Nutrient medium (5 ml) should preferably be inoculated with the patient's blood straight at the bedside. From 5 to 10 drops of the material should be added to each test tube. A 4-ml specimen of blood is defibrinated and injected to guinea pigs and 2-3 week-old rabbits (0.5-2 ml).

Diagnosis

Cerebrospinal fluid is examined in the presence of indications.

The urine is taken in sterile conditions (0.5-1 ml) on the second week of the disease and later. Nutrient media are inoculated with the urine in 3-4 test tubes.
Blood (2 ml) is tested in the laboratory on the 7-8th day: microscopic agglutination and lysis reactions are carried out with live leptospira cultures; the complement fixation test is also performed. Paired serums should be tested because the specific antibodies persist in convalescents from few months to several years.

Direct haemagglutination test and the immunofluorescent method are also used.

Treatment

Treatment should be early and complex.
Mild forms can be treated symptomatically and by proper diet and vitamins.
Mild and moderate diseases should be treated with penicillin
(3 000000-4000000 U daily intramuscularly until body temperature normalizes and then for 2-3 days more).
Detoxication therapy is also necessary. Severe forms should be treated with penicillin in doses to 10-16 million U daily.
Polyvalent leptospiral immunoglobulin
containing antibodies to common leptospiras, that are pathogenic to man, should also be administered. Immunoglobulin is first tested for tolerance by the patient and then administered intramuscularly in doses of 3 ml for children from 8 to 13 years of age, and 5-10 ml for older children and adults. Treatment continues for 3 days. In the presence of symptoms of cardiovascular insufficiency, cardiotonics and glucocorticoids are prescribed.

Treatment

In cases with acute renal failure and oliguria, a 20 per cent mannitol solution (300 ml), a 20 per cent glucose solution (500 ml), and a 4 per cent sodium bicarbonate solution (150-200 ml) should be administered by drip infusion in two sessions. The anuria stage of acute renal failure should be treated with haemodialysis (artificial kidney apparatus).

Haemorrhagic Fevers

This is a group of disorders of viral aetiology associated with natural nidality. The virus damages the endothelium of capillaries, arterioles and venules.
The most important clinical sign of a haemorrhagic fever is the haemorrhagic syndrome manifested by rash and haemorrhages in the skin and mucosa, bleedings of various location (nasal, gastrointestinal, uterine, renal, etc.). All haemorrhagic fevers are acute diseases characterized by fever and marked toxaemia. Renal involvement is characteristic. It is more marked in haemorrhagic fever associated with the renal syndrome. In most haemorrhagic fevers, blood changes are characterized by thrombocytopenia and leucopenia. The haemorrhagic fever with the renal syndrome is manifested by leucopenia during the first days of the disease, with development of the renal syndrome (leucocytosis, neutrophilosis with the shift to the left).

Haemorrhagic Fevers

At the present time, 12 nosologic forms of haemorrhagic fever are known. They are differentiated by the names of areas where they are first revealed. According to Chumakov (1974, 1977) and Simpson (1978), the following fevers are distinguished.

Tick-borne haemorrhagic fevers:

- Crimean-Congo haemorrhagic fever,
- Omsk haemorrhagic fever,
- Kyasanur forest disease;

Mosquito-borne haemorrhagic fevers:

- yellow fever,
- dengue haemorrhagic fever,
- Chikungunya haemorrhagic fever,
- Rift Valley fever;

Contagious zoonotic haemorrhagic fevers:

- haemorrhagic fever with renal syndrome,
- Argentinian haemorrhagic fever,
- Bolivian haemorrhagic fever,
- Lassa fever,
- Marburg haemorrhagic fevers.
- Ebola haemorrhagic fevers.

Haemorrhagic Fever with Renal Syndrome

- **Aetiology.** The disease is caused by the arbovirus. The virus is unstable in the environment; it circulates with the blood, and is excreted with the urine of patients during the entire fever period. In the laboratory, the virus propagates in trypsinized cultures of human embryo kidney cells. It can be detected by the immunofluorescent test.

Epidemiology

The source of infection are voles, field and wood mice, rats and other rodents.

They excrete the virus with their faeces, urine and saliva. Humans are infected by contact with the rodents or their excrements, by ingesting food contaminated with infected rodent excrements, or by inhaling dust containing such excrements.

Primary and secondary foci of haemorrhagic fever with renal syndrome are distinguished. In primary (sylvatic) foci, the disease occurs the whole year round with a peak during the warm season due to intensified activity of people in forests (picking up of berries, mushrooms, or nuts, fishing, hunting, etc.).

Epidemiology

In secondary foci the disease occurs during the warm season and the first cold months, which is associated with migration of rodents to human dwellings.

Infection can also be due to occupational exposure of agricultural workers.

Haemorrhagic fever with renal syndrome occurs usually as sporadic cases but epidemic outbreaks among newcomers are possible. Natural nidi of haemorrhagic fever with renal syndrome occur in Japan, Korea, China, Hungary, Bulgaria, Romania, Finland, Sweden, Norway, and Denmark.

Human susceptibility to the disease is high. Stable immunity is produced in those who sustained the disease.

Pathogenesis

The portal of entry are damaged skin and mucosa of the eyes, lips, and the mouth. The virus multiplies inside the cells and is released into the blood (viraemia phase). The pathogenesis is based on toxaemia and capillary damage, which are manifested by haemorrhagic rash, multiple haemorrhages, oedema and lesion of tissues of the internal organs, and the central nervous system. The advanced stage of the disease is characterized by hypothalamopituitary-adrenal insufficiency and severe septic shock. Damaged vessels and changes in the blood coagulation system cause haemorrhage. Renal lesion is manifested by changes in the urine and upset excretory function, which is due to the direct action on the renal vessels. Involvement of the renal vessels causes sero-haemorrhagic oedema, compression of the tubules, destruction of the tubular and glomerular epithelium, and oliguria. Desquamation of the tubular epithelium can lead to tubular obstruction and anuria.

Clinical picture

The incubation period lasts from 7 to 45 days,
usually 13-15 days.

Four periods are distinguished in a typical course
of the disease: fever, oliguria, polyuria, and recovery.

The onset of the disease is acute. It begins with a shaking chill and elevation of temperature to 39-40 °C where it remains for 5-6 days.

The patient is first excited, he complains of insomnia, headache,
pain in the eyes, muscles and abdomen, thirst, vomiting, and
lassitude. Excitation is then followed by flaccidity, apathy, and
sometimes delirium. Examination reveals hyperaemic face, fauces,
neck, conjunctiva and the sclera.

On the 3rd or 4th day (the beginning of the oliguria period), punctate roseoles and petechiae appear. Epistaxis and gingival bleeding develop; in severe cases, uterine, pulmonary and intestinal bleedings are possible. Leucopenia,
thrombocytopenia develop; ESR is low.

Clinical picture

The renal syndrome is pronounced: severe abdominal and lumbar pain, highly positive Pasternatsky's symptom. Oliguria develops (from 30 to 900 ml a day). Anuria is less common. The urine contains protein, red and white blood cells, and hyaline casts. Oedema is absent. By the moment when the renal syndrome develops, the temperature falls but the patient's condition worsens: vomiting and thirst increase, arterial pressure falls, in severe cases residual nitrogen in the blood increases to 2 g/l and more. The protein of the urine varies from 0.003 to 40 g/l.

Clinical picture

With development of the renal syndrome, the blood composition changes: leucocyte count increases to 10-30 x 109/1, neutrophilosis develops with the shift to the left, ESR accelerates. On the 9th-13th day (the onset of the polyuria period) the daily diuresis increases to 3-5 litres. The specific gravity of the urine decreases to 1.001-1.003. The amount of protein in the urine decreases too. The patient's condition improves: vomiting ceases, appetite appears, but the patient remains weak and thirsty. Dry mouth, dyspnoea and palpitation remain.

During the recovery period, polyuria decreases, and the patient's condition gradually improves.

The disease can run mild, moderately severe and severe course. The most severe forms of the disease occur in the Far East.

Complications

The specific complications are massive bleedings, haemorrhages into the brain, adrenal glands, pancreas, and myocardium. Septic shock, acute cardiovascular failure with lung oedema, azotaemic uraemia, rupture of the kidney and other complications are possible. Secondary infection can develop.

Diagnosis

The diagnosis is based on clinical and epidemiologic findings. Blood counts and urinalysis, as related to the periods of the disease, are important. Urine changes are specific and more demonstrative in the oliguria period: proteinuria to 40 g/l and higher, haematuria, cylindruria.
Laboratory diagnosis includes isolation of the virus (during the viraemia period) from the patient's blood and urine or tissues (inoculation into the cell culture, newborn albino mice, electron microscopy). Serologic tests are also important. Indirect immunofluorescent test, complement fixation test, passive haemagglutination inhibition test, diffuse precipitation in agar, and other reactions are used. Blood specimens, 2-5 ml, are taken for the purpose. Serologic tests can reveal the antibodies in the end of the first or early in the second week of the disease and later.

Treatment

Specific therapy is unknown.

Severe cases should be hospitalized in departments equipped with an artificial-kidney apparatus.

The patient must remain in bed for 3-4 weeks and more in severe cases, and for 2-3 weeks in diseases of moderate severity. Milk and vegetable diet is recommended. Salt is not restricted. Drinking much liquid is desirable.

During the fever period, the patient must be given vitamins B12, PP (nicotinamide), P (rutin), K (vikasol), ascorbic acid in large doses.

In order to decrease sensitization of the patient, pipolphen (0.025 g once a day) and dimedrol (0.03-0.05 g 2-3 times a day) should be given. Heparin (500 U per kg body weight) should be given to improve renal haemodynamics.

Treatment

Detoxication of the patient and correction of acid-base balance are attained by isotonic sodium chloride solution, glucose, and haemodez. Vascular insufficiency should be treated by infusions of plasma (200-300 ml), 5 per cent of albumin, and rheopolyglucin. In the presence of recurrent vomiting and anuria or in threatened septic shock, prednisolone and hydrocortisone should be given.

If heart failure develops, strophanthin or corglycon are given intravenously in divided doses. Analgin, pantopon, and dimedrol should be given for pain. Antibiotics should be given for secondary infections. Convalescents should be observed in outpatient conditions for a year.