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Treatment of Argentine hemorrhagic fever

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Abstract

Argentine hemorrhagic fever (AHF) is a rodent-borne illness caused by the arenavirus Junin that is endemic to the humid pampas of Argentina. AHF has had significant morbidity since its emergence in the 1950s, with a case-fatality rate of the illness without treatment between 15% and 30%. The use of a live attenuated vaccine has markedly reduced the incidence of AHF. Present specific therapy involves the transfusion of immune plasma in defined doses of neutralizing antibodies during the prodromal phase of illness. However, alternative forms of treatment are called for due to current difficulties in early detection of AHF, related to its decrease in incidence, troubles in maintaining adequate stocks of immune plasma, and the absence of effective therapies for severely ill patients that progress to a neurologic–hemorrhagic phase. Ribavirin might be a substitute for immune plasma, provided that the supply is guaranteed. Immune immunoglobulin or monoclonal antibodies should also be considered. New therapeutic options such as those being developed for systemic inflammatory syndromes should also be valuated in severe forms of AHF.

Keywords: Argentine hemorrhagic fever; Viral hemorrhagic fever; Arenavirus; Junin virus

1. Introduction

Argentine hemorrhagic fever (AHF) is a severe viral hemorrhagic fever endemic to the fertile farming plain of central Argentina, the "humid pampas" (Fig. 1) (Maiztegui, 1975). Junin virus (family Arenaviridae), the etiologic agent of AHF, is a rodent-borne virus. *Calomys musculinus* has been identified as its principal reservoir. Human exposure to Junin virus is believed to occur through inhalation of aerosolized body fluids or excretions of infected rodents, typically during agricultural work.

The emergence of AHF in the 1950s is hypothesized to have resulted from human alterations of the habitat in relation to agricultural practices. Such changes in the environment are reported to have favored the population growth of *C. musculinus*. Since the recognition of the illness, annual outbreaks have been registered without interruption, with number of cases between 300 and 1000, approximately. With the availability of an effective live attenuated Junin virus vaccine, a consistent reduction in the incidence of AHF was achieved in the 1990s (Enria and Barrera Oro, 2002; Enria et al., 2004). The objective of this article is to review knowledge acquired on the treatment of this illness and to discuss future expectations.

2. Clinical disease in AHF

The incubation period is usually from 6 to 14 days. Most infections with Junin virus (80%) result in clinical disease. Three phases are recognized in the illness: prodromal, neurological–hemorrhagic, and convalescence (Enria et al., 2004).

Prodromal phase: This phase lasts for the first week from onset of symptoms. The onset is insidious, with chills, malaise, anorexia, headache, myalgia centered particularly over the lower back, and moderate hyperthermia (38–39 °C). Other common symptoms include retro-orbital pain, nausea or vomiting, epigastric pain, photophobia, dizziness, constipation or mild diarrhea. Physical examination reveals flushing of the face, neck and upper chest; conjunctival congestion and periorbital edema. The gums look congested and may bleed spontaneously or under slight pressure. Over the soft palate, an enanthem represented by petechiae and small vesicles is almost constantly found. Typically, the patients have cutaneous petechiae in the axillary

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Fig. 1. AHF endemic area and last geographic extension.

regions, upper chest and arms. Lymph nodes in the laterocervical regions are enlarged. Generally, no signs of pulmonary abnormalities are detected. Relative bradycardia and orthostatic hypotension are frequently found. Hepatomegaly, splenomegaly and jaundice are very rare. At the end of this phase the patient may be irritable, lethargic, and with a fine tremor of the hand and tongue. Moderate ataxia, cutaneous hyperesthesia, and a decrease in deep tendon reflexes and muscular tonicity are present. In females, the presence of metrorrhagia is characteristic. Superimposed oral candidiasis is frequently found at the end of this phase.

Neurologic–hemorrhagic phase: Around 20–30% of the cases with AHF between 8 and 12 days after onset of symptoms enter in this phase, presenting severe hemorrhagic or neurologic manifestations, shock and superimposed bacterial infections. Hemorrhagic signs include hematemesis, melena, hemoptysis, epistaxis, hematomas, metrorrhagia and hematuria. Neurological involvement begins with mental confusion, marked ataxia, increased irritability and tremors that are followed by delirium, generalized convulsions and coma. Superimposed bacterial infections, presenting as pneumonia and septicemia may complicate the disease during this period. Acute renal failure is uncommon, but may appear in this phase in terminal cases, usually after prolonged periods of shock, as a consequence of an acute tubular necrosis.

Convalescence phase: Surviving cases experience a prolonged, protracted convalescence that lasts from 1 to 3 months. Patients experience asthenia, irritability, memory changes and hair loss. Around 10% of the cases treated with immune plasma develop a late neurological syndrome (LNS). This LNS begins after a period free of symptoms, and is characterized by febrile symptoms, cerebellar signs and cranial nerve palsies (Enria et al., 2004; Enria, 2005). No cases of LNS have been registered among AHF patients who have recovered without specific treatment (Maiztegui et al., 1979; Enria et al., 1985). A single case has been observed in a patient who was treated late in the course of the illness with intravenous ribavirin (Enria et al., 1987).

Clinical laboratory studies: During the first week of the illness, there is a progressive leucopenia and thrombocytopenia, with counts around 1000–2000 white cell and 50,000–100,000 platelets per mm^3. The sedimentation rate is normal or decreased. There is proteinuria, and urinary sediment containing hyaline-granular casts and red blood cells. Elevations in aspartate transaminase (AST), creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) are common, but mild. Serum creatinine and urea are generally normal, but are increased in severe cases in proportion to dehydration and shock.

During the acute illness, cerebrospinal fluid (CSF) is normal, even in patients with a severe neurological form. However, the CSF in patients with LNS showed a moderate increase in the number of cells, with normal sugar; normal to moderate increase in the number of cells and the presence of antibodies against Junin virus in titers that exceed the 1:40 ratio compared with those in the serum (Enria et al., 2004; Enria, 2005).

3. Pathogenesis and immunology

As noted, most cases of AHF are believed to result from inhalation of virus-containing material from infected rodents. Viral replication is thought to occur at the initial site of infection, generally the lungs, with subsequent dissemination to other parenchymal tissues. A wide variety of organs may be affected, including vascular endothelium, myocardium, kidneys and the central nervous system (Buchmeier et al., 2006). Gross pathologic changes are generalized but non-specific (Maiztegui, 1975).

The bleeding seen in AHF is considered the result of thrombocytopenia, abnormal platelet function induced by a plasma component, and alterations in blood coagulation with fibrinolysis activation (Marta et al., 2000). Haemostatic abnormalities include prolongation of activated partial thromboplastin time (APTT), low levels of factors VIII, and IX; increased values of factor V, von Willebrand factor, and fibrinogen; decreases in antithrombin III and plasminogen. Endothelial cell involvement is shown by increased levels of von Willebrand factor (Heller et al., 1995).

In AHF, viremia is present throughout the acute febrile period. Very high titers of endogenous interferon-α (IFN-α) have been demonstrated accompanying viremia (Levis et al., 1984, 1985). The levels of IFN-α decreased after the transfusion of immune plasma. Tumor necrosis factor-α (TNF-α) titers are also increased (Heller et al., 1992).

During the prodromal and the neurological–hemorrhagic phases, there is an acute transitory immunodeficiency. This