Smallpox: A Renewed Public Health Concern

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Abstract

Smallpox is a viral disease unique to humans. The last naturally occurring case of smallpox was diagnosed in 1977. There is now rising concern that smallpox may be used as a biological weapon. Large scale smallpox vaccinations have not been carried out for over 30 years and there is evidence suggesting that those immunized several decades ago no longer have sufficient levels of circulating antibodies to confer protection. While there is no known treatment for the smallpox infection, a potential outbreak may be considerably controlled through rapid identification of the pathogen, isolation of those infected and selective immunization of contacts and health personnel.

Introduction

Smallpox is a uniquely human viral disease with a lengthy history. It has long been regarded as one of the most deadly of infectious diseases due to its high mortality rate and ease of transmission. Variola, the virus that causes smallpox, was once endemic throughout most of the world. Before the widespread use of vaccination, nearly all people were exposed to the disease at some point in their lives. In 1967, the World Health Organization (WHO) began a global campaign to eradicate smallpox. The last naturally occurring case was diagnosed in Somalia on October 26, 1977. On May 8, 1980, the WHO declared the world free from smallpox; one of the greatest success stories in the history of public health. A disease which had caused tremendous human morbidity and mortality for thousands of years was eradicated only 13 years after the initiation of the WHO program. Even prior to the events of September 11, 2001, concern had been expressed over the implications of the use of variola as a biological weapon against a largely susceptible population. The use of this disease in a deliberate attack against human beings must now be considered a remote but real possibility.

History

The earliest evidence of smallpox comes from pockmarks on an Egyptian mummy dated to 1600 BC.[1] The first recorded smallpox epidemic occurred in 1350 BC during the Egyptian-Hittite war.[2] The disease reached Europe between the 5th and 7th centuries and was first recorded in the New World in 1507. Each time variola encountered a new population with no previous immunity huge numbers of human lives were lost. Smallpox was first used as a biological weapon in the 1760s by British soldiers in North America during the French and Indian Wars.[3] Blankets that had been used by smallpox patients were distributed among the Iroquois and the resulting epidemics killed more than 50% of affected tribes.

Before the development of the cowpox vaccine, the technique of variolation was practiced in parts of Asia and Africa. In China, dried smallpox crusts were inserted into the nostrils. In other regions, fluid from a smallpox pustule was rubbed into a small scratch on the arm.[4] Both of these methods produced a much milder form of the disease and conferred lifelong immunity. However, Europeans did not immediately adopt the practice of variolation. It was not until Lady Mary Wortley Montagu, wife of the British Ambassador to Turkey, variolated her young son at Adrianople in 1718 that variolation became an accepted practice in Europe.[4] The use of variolation was first recorded in Canada in 1765.[4]

Late in the 18th century, Edward Jenner observed that milkmaids who had contracted the closely related disease cowpox were immune from the much more lethal smallpox. He subsequently developed the smallpox vaccine that would remain in use for 200 years.[2] In Canada, the vaccine was produced by Dr. Alexander Stewart using his own cattle until 1916, when manufacturing was taken over by Connaught Laboratories.[4] Endemic smallpox was eradicated in Canada by 1946. The last confirmed Canadian case, in 1962, was in a teen that had arrived from Brazil.[5]

In 1980, the WHO recommended that all countries cease smallpox vaccination. All remaining variola virus were stored at either the US Centers for Disease Control and Prevention (CDC) in Atlanta or the Russian State Research Centre of Virology and Biotechnology, in Koltsovo.[6] Beginning in 1996, the World Health Assembly (the WHA meets yearly and is attended by delegations from all Member States of the WHO) has recommended several times that all remaining virus stores be destroyed, however, this has not yet been carried out. In May 1999, the WHA authorized tem-

porary retention of current viral stocks until no later than 2002 for the purposes of further international research.[6] This decision was made after reports from a former deputy director of the Soviet Union's civilian biological weapons program that in 1980, the Soviet government commenced a successful program to develop large amounts of smallpox virus and adapted the virus for use in bombs and missiles. Further allegations stated that research continues even today into the development of more virulent and recombinant strains.[3] The disintegration of the former USSR and financial woes in the new Russia have prompted fear that Soviet developed biological weapon technology may fall into non-Russian hands. It has also been recognized that advances in polymerase chain reaction technology has made it possible to recover fragments of smallpox virus from inactivated material such as irradiated, killed virus, or formalin-treated infected tissue.[7] Many such sources of variola DNA exist around the world.

Microbiology

The variola virus is a double stranded DNA virus and a member of the genus orthopoxvirus.[8] This genus also includes monkeypox, vaccinia, and cowpox which can all infect both animals and humans. The orthopoxviruses belong to the poxvirus family. The poxviruses are among the largest viruses in existence. On electron microscopy, the poxviruses are oval or brick shaped and measure 200 to 400 nm.

Pathogenesis

Infection with the variola virus follows inhalation and implantation in the respiratory or oropharyngeal mucosa. The infectious dose is believed to be only a few virions.[3] All poxviruses replicate in the cytoplasm of cells. Soon after infection, early and late virion proteins and enzymes are produced. The replication sites are separate from the host nucleus and replication machinery.[8] The virus first replicates in regional lymph nodes and by day three or four of infection, an asymptomatic viremia develops. The virus then begins to replicate in the spleen, bone marrow and systemic lymph nodes. By day 8, a secondary viremia develops. Shortly thereafter, the patient becomes symptomatic.

Clinical Presentation

The incubation period of smallpox is 12 to 14 days. Following this period, the patient becomes febrile, has severe aching pains, malaise, and develops a headache and backache. Abdominal pains and delirium may be present. A rash develops over the face and forearms and spreads to the trunk. Over the course of 8-10 days, the rash evolves from macular to papular to vesicular to pustular and finally crusts. The period of greatest infectivity is during the first week of illness. This is the time of greatest virus titres in the saliva. The mortality of smallpox infection is approximately 30%. Death usually occurs in the second week and is likely the result of toxemia caused by circulating immune complexes and soluble viral antigen.[3] Patients who recover often have severe scarring of the face from destruction of sebaceous glands, followed by shrinkage of granulation tissue. In other cases, corneal infection can lead to blindness.[3]

In 5% to 10% of variola infections, the disease progresses rapidly to the nearly always fatal malignant form. In these patients the lesions become extraordinarily dense, and bleeding into the skin and intestinal tract can occur. These cases are extremely infective and death occurs within 5 to 7 days.[9]

Diagnosis

The disease most easily confused with smallpox is chickenpox (varicella). A key diagnostic feature in smallpox is that all lesions are at the same stage of development. This is in contrast to chickenpox in which the patient presents with lesions in different stages of development. While chickenpox lesions are most dense on the trunk, smallpox lesions are most dense on the face and extremities. In variola infection the lesions are deeper than in varicella.

If tests for other diseases prove negative and smallpox is suspected, an individual who has recently been vaccinated, and is wearing gloves and a mask, should collect specimens. In Canada, laboratory analysis should be conducted in the level 4 facility located in Winnipeg. It has been suggested that a two-week time frame for the positive identification of a primary smallpox infection may be optimistic.[10] Once smallpox has been confirmed, future diagnoses may be made on clinical grounds.

Prevention, Treatment, and Infection Control

Routine vaccination against smallpox in North America was stopped in the early 1970s. The immune status of those who received vaccination over 30 years ago is unknown. It has been shown, however, that in those who received a single vaccination, antibodies significantly decline after 5 to 10 years.[3] It therefore must be assumed that the Canadian population is highly susceptible to infection. While the WHO and a number of countries around the world have stockpiled the smallpox vaccine, there are currently no manufacturers who would be able to produce large quantities in an emergency situtation.[11]

A single confirmed case of smallpox should be considered an international health emergency. If smallpox is suspected, local, provincial, and federal public health authorities must be notified immediately. There is no cure for smallpox infection. Recent evidence[6] has indicated that the anti-viral cidofovir may prove to be an effective treatment but further research is required. All cases should be isolated in negative pressure rooms with a fine particulate air filtration system. Antibiotics are given for possible concurrent bacterial infection and supportive therapy is initiated. Vaccination within four days post exposure may prevent or decrease the severity of infection. As soon the diagnosis is made, all household and face-to-face contacts should receive vaccination. In the event of an outbreak, all hospital staff should be immediately vaccinated as well as those likely to be involved in the response such as police, fire personnel and mortuary workers. Vaccination is not without risk. Adverse reactions occur in a small number of people who receive the smallpox vaccine. Postvaccinal encephalitis occurs once in 3 per million primary vaccines; 40% of these cases are fatal and others are left with permanent neurological sequelae. Progressive vaccinia may occur in those who are immunocompromised from a congenital defect, drugs, malignancy, radiation therapy, or AIDS.[9] In these individuals, the vaccinia virus simply continues to grow.

Treatment involves the administration of immune globulin. It is likely that the rate of adverse reactions would be higher than that seen during prior smallpox immunization programs due to the increased numbers of immunosuppressed individuals.

Summary

Smallpox represents a serious threat as a biological weapon because of high population susceptibility, high infectivity and mortality rate, and lack of effective treatment. The potential for catastrophe is real unless effective control measures can be quickly implemented. Early diagnosis is essential to minimize contacts prior to the commencement of vaccinations. In order to do this, health care professionals must be educated about a disease that they have not seen clinically in over two decades. The development of a rapid diagnostic kit to identify the variola virus during the prodrome would considerably speed the recognition of this disease and the initiation of the response. Issues such as quarantine, information dissemination and coordinating the response effort must be discussed prior to an emergency situation so that confusion and panic is minimized. Finally, it is essential that the existing stocks of vaccine are increased and that there exist means of effective distribution. Even with increased vaccine stores, demand would likely overwhelm supply. It must be ensured that limited vaccine stores are used optimally. A focused selective vaccination series is an essential part of a control program. While the prospect of a smallpox epidemic is certainly frightening, the damage may be limited with a timely and directed response.

References

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Poem

An Inventor of Bones

Taken from a Student's notebook.
(Subscribed by Dr. S. M. Hay, Class of 1885).

Reprinted from the UTMJ (1941) 18: 184.

"How many bones in the human face?
Fourteen, when they're all in place.
How many bones in the human head?
Eight, my child, as I've often said.
How many bones in the human ear?
Four in each, and they help to hear.
How many bones in the human spine?
Twenty-four like a climbing vine.
How many bones the shoulder bind?
Two in each--one before, one behind.
How many bones in the human arm?
In each arm one; two in each forearm.
How many bones in the human wrist?
Eight in each, if none are missed.
How many bones in the fingers ten?
Twenty-eight, and by joints they bend.
How many bones in the human hip?
One in each; like a dish they dip.
How many bones in the human thigh?
One in each and deep they lie.
How many bones in the leg from the knee?
Two in each we can plainly see.
How many bones in the ankle strong?
Seven in each but none are long."