



FACT SHEET

Smallpox (variola virus)

Pathogen: Pox viruses

Smallpox is a contagious diseases caused by the variola virus, part of the orthopoxvirus genus, which itself is a member of the poxviridae family of viruses. Infection with other members of this family, such as monkeypox, cowpox, camelpox and vaccinia viruses, has less serious consequences for humans; the smallpox vaccine, for example, contains the vaccinia virus. Orthopox viruses are genetically very similar; the camelpox and variola viruses share 85% of their nucleotides. These viruses also share a very similar morphology, making it difficult to distinguish between them, even under an electron microscope. Orthopox viruses measure approx. 260 nm x 150 nm, making them one of the largest known viral genomes. The DNA strand of the genome consists of approx. 200,000 based pairs, which contains the genetic coding of around 200 different proteins. The genomic DNA is held inside a protein capsule, the capsid, which itself is surrounded by a virus envelope of membrane proteins. Orthopox viruses multiply in the cell cytoplasm and exit the host cell by a process of lysis (i.e the cell dies when the cell membrane ruptures). The smallpox virus has two main forms: variola major and variola minor. The clinical features of each of these differ.

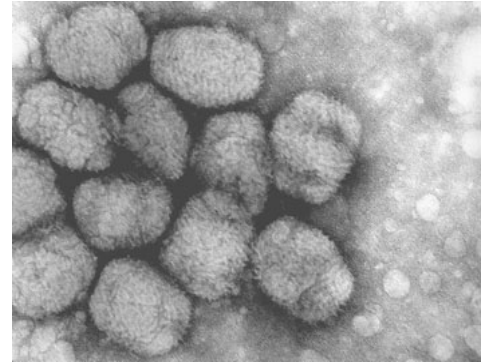


Image: Variola virus

Source: © 2003 - 2007, Sutter County, California

Occurrence

Thanks to the WHO vaccination campaign, smallpox was eradicated worldwide. The last natural case of smallpox occurred in Somalia in 1977. However, a fatal laboratory-acquired case occurred in England in 1978. Since then, only two laboratories now have samples of the virus (CDC Atlanta in the United States and the Vector Institute in Russia). Smallpox was one of the most devastating contagious diseases in the world, killing 30% of all those who were infected. As late as the 18th century, smallpox killed every tenth child born in Europe. In 1798, the tentative hope that the disease could be finally controlled emerged when Edward Jenner demonstrated that inoculation with cowpox could protect humans against the smallpox virus. Even in the early 1950s, 150 years after vaccination was introduced, there were around 50 million smallpox cases worldwide. In 1967, when the WHO launched its global eradication campaign, the number of smallpox cases was still around 10-15 million. Thanks to this campaign, the global eradication of smallpox could finally be declared.

Transmission

Humans who had not been vaccinated were highly susceptible to infection from the variola viruses. Humans are the only reservoirs for these viruses; there is no animal reservoir and the virus cannot be transmitted via insects. Person-to-person transmission was primarily due to infection via aerosols expelled when the infected person coughed or as the result of face-to-face contact with the patient, especially during the fever stage and in the first week follow-

ing the appearance of the tell-tale rash. The virus could also be spread by contaminated clothes and bedding, though the risk of infection from this pathway was much lower. Patients who contracted the more common and severe form of smallpox (variola major) were often so ill (i.e. bed-ridden) that the spread of infection was limited to those who were in closest contact with them. Because the symptoms of variola minor were milder, the virus was able to spread more widely. During the eradication campaign, investigations found that the virus could be transmitted via ventilation systems and infect people who were not in the immediate vicinity of the infected person.

Epidemics develop relatively slowly. The interval between each generation of cases was around two to three weeks. When a natural outbreak occurred, an infected person (index case) transmitted the virus to a maximum of five others. Given that these data are available only for periods with substantial population immunity to smallpox and that vaccination has now ceased, the world's population would be more susceptible to the virus. Some experts reckon that the transmission rate today would be around 10 new infections per index case.

Aetiopathology (symptoms)

There are two main forms of smallpox: variola major and variola minor. Both cause skin lesions, although the symptoms of variola minor are considerably milder and are fatal in only 1% of cases. However, the mortality rate of variola major is 30%. There are two more forms, albeit much rarer ones: haemorrhagic and malignant. The first is characterised by bleeding in the mucous membranes and the skin. The second, "flat-type" malignant smallpox, is characterised by lesions that remain soft and flat. The fatality rate for both these forms is high. A modified form of pox also occurs in people who have been vaccinated against smallpox.



Image: Generalised smallpox

www.gapinfo.de/gesundheitsamt/alle/seuche/infekt/viru/pocken/mb/bild.htm

The incubation period of smallpox is usually between 12 and 14 days (range 7-17). During this phase, there is no evidence of viral shedding. Patients feel well and are not contagious. The incubation period is followed by the sudden onset of flu-like symptoms: fever, feeling unwell, headache, back pain and, in some cases, stomach pains and vomiting. Two to three days later, body temperature drops and the patient begins to feel better, at which point tiny red spots often appear on the tongue, gums, mouth and oropharynx. 24 hours later, these develop into a pustule-like rash. Lesions on the mucous membranes release large amounts of the virus into the mouth and throat, making the patient highly contagious. At the same time, the rash characteristic of smallpox appears, first on the face, then on the hands and forearms, before spreading to the entire body. The diagnostic feature of smallpox is the centrifugal distribution of lesions which are more prominent on the face and on the extremities. The rash also typically affects the palms and soles. All lesions on the given part of the body progress in the same way: small pink spots - raised papules - vesicles with a small indentation in the centre - pustules. Eight to fourteen days after the onset of symptoms, the pustules form scabs which on healing leave deep, depigmented scars, i.e. the characteristic "pockmarks". The disease is fatal primarily when the patient presents with haemorrhagic manifestations (bleeding in the skin and mucous membranes prior to the formation of pustule), and when there is a general systemic deterioration, caused by blood poisoning and the formation of immunocomplexes (virus and antibody complex). It is also not uncommon for a patient to present with bronchial pneumonia as well as an attendant bacterial lung infection, or with viral encephalitis (inflammation of the brain). Smallpox survivors are often recognisable by the deep, pitted scars which are left behind. Blindness is also a common complication.

Identification (diagnosis)

From a clinical point of view, it is important to distinguish actual smallpox from chickenpox (varicella zoster virus), the herpes simplex virus, scarlet fever and less dangerous pox viruses (cowpox, vaccinia and parapox). A differential diagnosis can be made by an experienced physician based on the distribution and appearance of the pustules. Pox viruses can also be identified by examining pustule specimens under an electron microscope. This will only distinguish orthopox viruses from herpes simplex and parapox; it will not differentiate between the different orthopox viruses (e.g. vaccinia). Reliable diagnosis is only reached with the use of validated molecular biology techniques (real-time PCR, PCR and sequencing). Growing the virus in chicken embryo cells according to typical growth patterns could also be helpful, but must be carried out in a Level 4 biocontainment laboratory (BSL-4). Antibodies may also be used to identify pox viruses, but it is almost impossible to distinguish between smallpox and other orthopox viruses. In terms of rapid diagnosis, serology, i.e. the detection of antibodies in the blood of the patient, is an effective technique, since antibodies develop at a relatively late stage and cross-react with other orthopox viruses.

Therapy

There is currently no effective causal treatment of smallpox; only the symptoms of the infection can be treated. Supportive therapy involves electrolyte and blood volume repletion, as well as the administration of antibiotics to treat any secondary bacterial infections. The effectiveness of a range of substances (e.g. cidifovir) against orthopox viruses have been tested, in some cases with promising results. However, it remains to be seen whether they would be effective against actual smallpox. Be that as it may, the administration of specific antibodies (Vaccinia Immunglobulin, VIG) can reduce the severity of the disease.

Prevention

To control the spread of a smallpox outbreak, the priority of any response plan must be ring vaccination (i.e. vaccinating anyone in a prescribe area who could be susceptible) and the isolation of those who are already infected. It should be remembered that patients are not infectious during the early stage of the disease. They only become infectious with the onset of fever, and remain so until the scabs have healed. Suspected cases must be physically isolated and all people with whom they have come into contact must be identified and vaccinated. Experiences from the WHO eradication campaign have shown that a strict monitoring system can break the chain of transmission, provided that there is a rapid response to new cases, that the necessary infrastructure to isolate patients is in place, and that everyone who has come into contact with the infected person can be vaccinated. However, epidemiological models show that the absence of immunity against smallpox in Europe would necessitate the vaccination of the entire population or, at the very least, of those in endemic regions so as to control the outbreak. Switzerland has stockpiled enough vaccine for the entire population. However, these are old vaccines containing the live vaccinia virus and have been in deep-freeze storage for decades. The vaccine may cause severe complications in certain population groups like the immuno-compromised, pregnant women, infants less than one year old and people with a history of eczema. Approximately 10-100 out of one million will suffer adverse effects, and one person out of this one million could die. A number of clinical studies are currently testing the tolerance to and immunogenicity of third-generation smallpox vaccines containing highly diluted viruses. The aim is the eventual replacement of the first-generation vaccine. Vaccination should offer good protection against smallpox infection for at least five years, and possibly for as long as 10 years.

In the event of a smallpox epidemic, the mandatory vaccination of the entire population will be introduced. The public will also be told to avoid large gatherings and to follow the instructions issued by the Federal Office for Public Health (FOPH). Schools and other institutions will be

shut down. Medical personnel as well as others who come into contact with infected patients and material must be equipped with adequate protective material (protective gloves, protective goggles and air inhalation masks [FFP-3], or special protective suits with ventilated hoods). Contaminated clothes and bedding must be incinerated or autoclaved. Rooms and objects can be sterilised using formaldehyde or perchloroacetic acid.

Smallpox as a biological weapon

Although smallpox has been globally eradicated, it is still considered as potentially one of the most dangerous biological weapons, because most of the global population has not been vaccinated against the virus and the immunity of those who have been vaccinated has dwindled. Since the virus no longer occurs naturally, other sources must be found. There are three possible sources. The first is frozen specimen material overlooked when other smallpox specimens were being destroyed and still stored somewhere in a laboratory freezer drawer. Given that the virus was found throughout the world before it was wiped out, it is entirely plausible that not all samples containing the virus have been destroyed. The second possible source is the biological agent storage depots in Russia. As a signatory state to the Biological Weapons Convention, the former Soviet Union had to undertake to destroy their stocks of biological agents. Given that many scientists found themselves out of work as a result, it is possible that certain rogue elements may have held on to some specimens. The third and most likely source is the synthesis of the virus. It has been repeatedly shown that a virus can be artificially manufactured and this would also apply undoubtedly to the smallpox virus. Although the genome of the smallpox virus is relatively large, its entire genetic sequence can be retrieved from the internet and the molecular biology techniques needed to synthesise the virus are now rather easy to come by.

The smallpox virus can be grown in cell cultures, then concentrated by means of centrifugation and finally frozen without much problem. The virus is not resistant to UV light, though a number of substances can be added to stabilise it. When dried, the virus remains infectious for a very long time. The virus can also be dispersed in aerosol form, e.g. through a building's ventilation system. This would infect a large number of people who would, after the onset of fever, go on to infect others.

The control of a smallpox outbreak will necessitate far-reaching immunisation programmes. Very few countries have stockpiled enough vaccine to immunise their entire population. Today, an outbreak could be caused by a terrorist attack. Of course, manufacturing viral warfare agents is not particularly easy, as it requires specialist expertise and the appropriate infrastructure (BSL-3/BSL-4-laboratory, incubator, access to molecular biology technologies). However, the commercialisation of these technologies coupled with easier access to information via the internet means that it is now considerably less difficult to manufacture genetically modified micro-organisms.

Given its relatively high infectivity, its ability to disperse via aerosols, its rather good environmental stability, its high pathogenicity and the absence of effective treatment, smallpox is justifiably considered as potentially one of the most dangerous bioweapons known to mankind.

Literature

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