Omsk haemorrhagic fever

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Omsk haemorrhagic fever is an acute viral disease prevalent in some regions of western Siberia in Russia. The symptoms of this disease include fever, headache, nausea, severe muscle pain, cough, and moderately severe haemorrhagic manifestations. A third of patients develop pneumonia, nephrosis, meningitis, or a combination of these complications. The only treatments available are for control of symptoms. No specific vaccine has been developed, although the vaccine against tick-borne encephalitis might provide a degree of protection against Omsk haemorrhagic fever virus. The virus is transmitted mainly by *Dermacentor reticulatus* ticks, but people are mainly infected after contact with infected muskrats (*Ondatra zibethicus*). Muskrats are very sensitive to Omsk haemorrhagic fever virus. The introduction of this species to Siberia in the 1930s probably led to viral emergence in this area, which had previously seemed free from the disease. Omsk haemorrhagic fever is, therefore, an example of a human disease that emerged owing to human-mediated disturbance of an ecological niche. We review the biological properties of the virus, and the epidemiological and clinical characteristics of Omsk haemorrhagic fever.

Introduction

In 1941, physicians in the northern lake-steppe and forest-steppe areas of Omsk region, Russia, started to note sporadic cases of an unusual acute febrile disease with symptoms of abundant bleeding from the nose, mouth, and uterus, and skin haemorrhage, haemorrhagic rash, and leucopenia. The greatest number of cases was recorded in May, 1946. The disease was initially misdiagnosed as various other diseases, such as typhoid form of tularaemia, typhus, paratyphus, bronchitis, pulmonary tuberculosis, or alimentary-toxic aleukia.[1] That the disorder had a previously unrecognised cause, however, soon became clear, and the name Omsk haemorrhagic fever was coined.[2] The geographical focality, seasonal pattern, and non-contagiousness of the disease were initially identified as defining characteristics. A remarkable correlation was noted between the seasonal activity of ticks and the numbers of cases, and a causal relation was suggested.[3] Later, however, a prominent pattern of contact with muskrats (*Ondatra zibethicus*; figure 1) was seen among new cases: outbreaks occurred most frequently in muskrat hunters and their family members who participated in removal and treatment of muskrat skins.[1]

The causative agent of this disease, Omsk haemorrhagic fever virus, was first isolated in 1947 during an expedition to the Omsk region by Russian scientists from the Omsk Institute for Natural Focal Infections and the Institute of Poliomyelitis and Viral Encephalitides, and with participation of local medical workers.[2,3] Several members of the expedition became infected with the virus, although all cases ended in recovery.[2] The viral origin of the disease was authenticated when the serum of patients in the first phase of the disease remained infectious for guineapigs even after filtering through Seitz or Berkefeld filters.[2] Later, the virus was successfully isolated from human patients and from meadow ticks *Dermacentor reticulatus* (figure 1). This tick was subsequently acknowledged as the main vector of Omsk haemorrhagic fever virus.[2,3]

Muskrats are an alien animal species to Russia that was brought to Siberia from Canada for industrial fur production purposes.[4] The first animals were released in 1928 in western Siberia along the Demyanka River, and in 1935 in the Novosibirsk region. During the peak period of introduction (1935–39), 4340 muskrats were released. Breeding, however, did not reach its economic potential in Siberia because of fatal epizootics. In 1946–70, 76 different epizootics were recorded in the Tjumen, Kurgan, Omsk, and Novosibirsk regions, which are on the borders of forest-steppe and lake-steppe zones (figure 2).[5] Omsk haemorrhagic fever virus is purported to have existed silently in Siberia before the muskrats' release, but the introduction of these highly susceptible animals is thought to have greatly amplified infection rates in other animals, including human beings.[6]

Since the first description of Omsk haemorrhagic fever in the 1940s, the clinical course, pathology, and epidemiology of the disease, as well as the ecology of the virus, vectors, and natural hosts, have been studied extensively. Most data, however, have been published in Russian-language journals and proceedings. Therefore, comprehensive English-language reviews on this disease are scarce. We provide a summary of the available data on the virological and biological properties of the causative organism and on the clinical and epidemiological features of Omsk haemorrhagic fever.

Search strategy and selection criteria

We searched PubMed for articles published in any language from 1948 onwards. The search terms "Omsk hemorrhagic fever" or "Omsk haemorrhagic fever" were used. We did further manual searches of the reference lists in identified articles and books. Data from primary articles, reviews, books, and book chapters published in Russian, English, Czech, and German are summarised in this Seminar.

Virology

Omsk haemorrhagic fever virus is classified as a member of the tick-borne group of flaviviruses within the family Flaviviridae.[7] Only three other tick-borne flaviviruses are known to cause haemorrhagic disease in human beings:

Kyasanur forest disease virus, which is endemic to southern India;[8] a variant of Kyasanur forest disease virus called Alkhurma virus, which has been isolated in Saudi Arabia;[9] and some strains of the Far Eastern subtype of tick-borne encephalitis virus, which occurs in the Novosibirsk region in Russia.[10] Phylogenetically, Omsk haemorrhagic fever virus is closely related to tick-borne encephalitis virus (figure 3) and the morphology, structural features, and mode of replication of the two organisms are similar.[11,12] However, Omsk haemorrhagic fever virus has evolved to have features that distinguish it from tick-borne encephalitis virus, and which seem to reflect the ecology of the steppe regions rather than the more-densely forested regions favoured by tick-borne encephalitis virus.[13]

The particles of the Omsk haemorrhagic fever virus are of spherical or polygonal shape, approximately 40 nm in diameter. In the centre of the virus particle is a dense nucleoid with a diameter of about 25 nm,[11,12] formed of a nucleocapsid composed of a positive-sense, single-stranded RNA genome enclosed in a capsid protein. The nucleocapsid is surrounded by a host-cell-derived lipid bilayer.[13]

Omsk haemorrhagic fever virus has a genome length of 10 787 bases with an open reading frame of 10 242 nucleotides that encode 3414 aminoacids. The open reading frame is flanked by 5′ and 3′ untranslated regions. The 5′ untranslated region of Omsk haemorrhagic fever virus contains a 5′-cap and has a stretch of about 30 nucleotides not generally seen in other tick-borne flaviviruses. The 3′ untranslated region is slightly shorter than that in other flaviviruses, but is similar in that it lacks a 3′-poly(A) tail, and is otherwise very close to those in the Far Eastern and Siberian strains of tick-borne encephalitis virus.[14] The open reading frame encodes a large polyprotein that is cleaved by cellular and viral proteases during and after translation into three structural proteins (C, prM, E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5).[13,15] The cleavage sites between viral proteins within the Omsk haemorrhagic fever virus open reading frame are completely conserved.[14]

Viral non-structural proteins, including the RNA-dependent RNA polymerase (NS5), serine protease (NS2B-NS3), and helicase (NS3), are involved in the replication machinery of the virus in a host cell.[15] In mammalian cell lines replication is generally associated with the formation of cytopathic effect,[16] which leads to alterations in the fine structure of the nucleus and the cytoplasm with the formation of oxyphilic cytoplasmic inclusions. Viral antigens localise in the perinuclear cytoplasm zone of infected cells. There is apparent proliferation and hypertrophy of membranous structures of the cell, which is similar to the situation in cells infected with tick-borne encephalitis virus.[17] Viral particles are distributed mostly in the reservoirs of the endoplasmic reticulum and Golgi complex.[11]

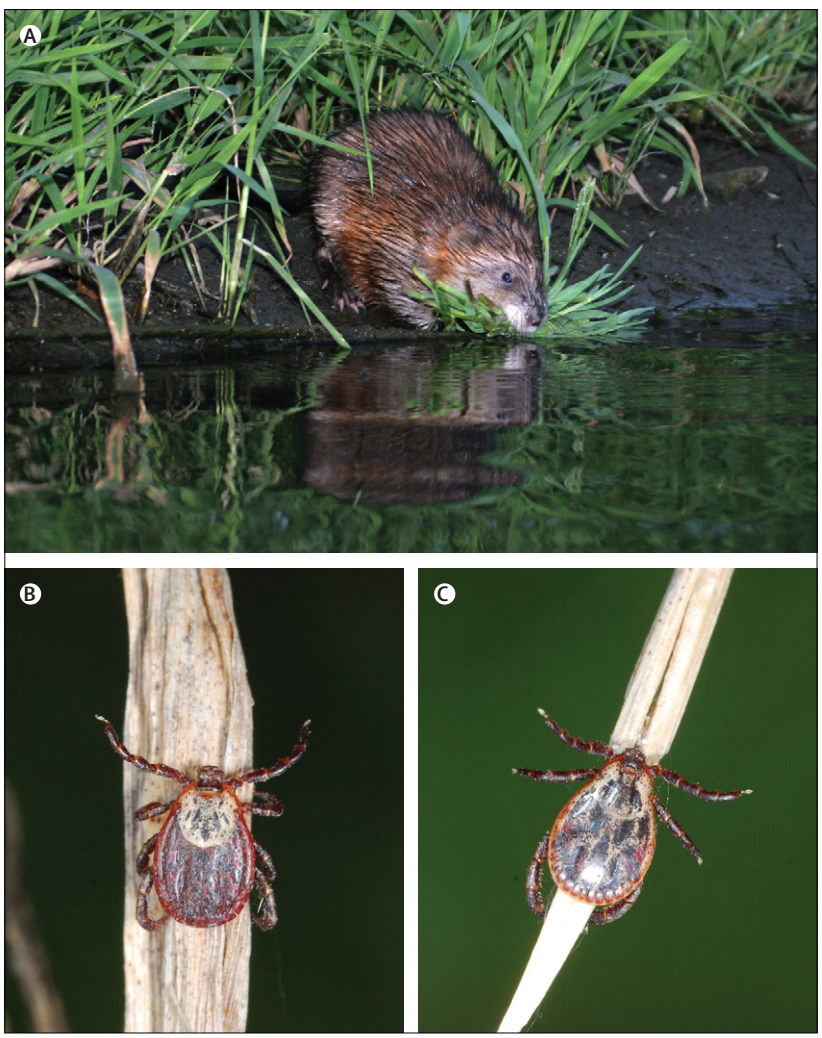

Figure 1: **Host and vectors of Omsk haemorrhagic fever virus**
(A) Muskrat (*Ondatra zibethicus*), the main amplifying host of Omsk haemorrhagic fever virus in nature. (B) Female and (C) male meadow ticks (*Dermacentor reticulatus*) are the main vectors of Omsk haemorrhagic fever virus. Photograph for A provided by by Silvestr Szabó, and for B and C by Dr David Modrý, with permission.

Genetically heterogeneous strains of Omsk haemorrhagic fever virus have been isolated, differing in plaque size, haemagglutination activity, and neurovirulence (figure 3).[18] With the use of polyclonal antibody absorption and haemagglutination assays, two subtypes of Omsk haemorrhagic fever virus were defined by Clarke[19] (strains Kubrin and Bogoluvovska). These results were, however, based on comparison of only four virus strains, and the two subtypes differed by only six nucleotides resulting in four aminoacid changes.[20] Three of these changes were present in the viral E protein and might determine antigenicity.[20] Kornilova and co-workers[21] compared larger numbers of isolates from different sources and reported three serotypes (two were the same as those found by Clarke and one was different) that differed in various factors, including cross-neutralisation, agar-gel immunodiffusion, dynamics of

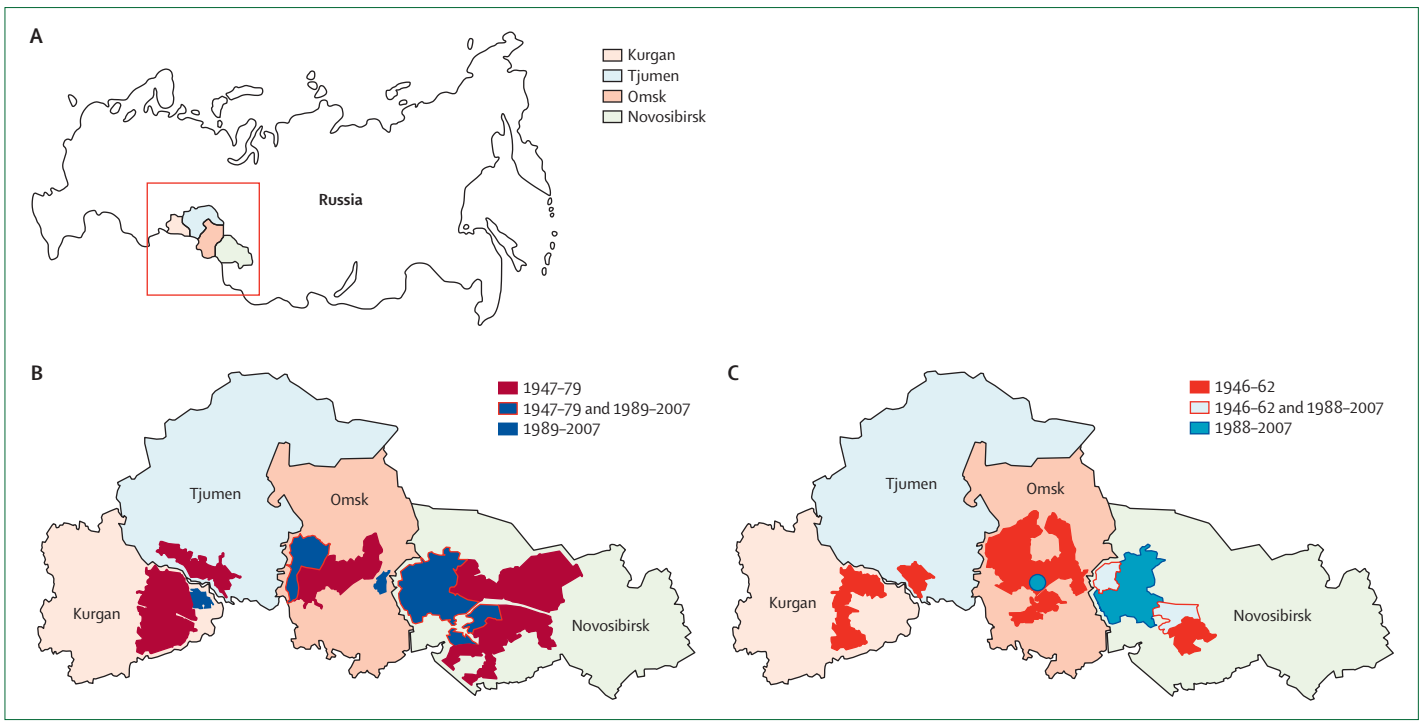

Figure 2: **Geographical distributions of Omsk haemorrhagic fever by year and region**
(A) Endemic administrative regions of Russia. (B) Epizootic of Omsk haemorrhagic fever in muskrats. (C) Human morbidity from Omsk haemorrhagic fever since 1946.

replication, haemagglutinin production in cell lines, and virulence for mice.

Ecology

The exact distribution of Omsk haemorrhagic fever virus in Siberia has not been fully determined; the available data are based only on reported human and muskrat infections. The disease was reported in the Omsk, Tjumen, Novosibirsk, and Kurgan regions (figure 2), but the involvement of other regions of western Siberia has been suggested.[13] Development and establishment of natural foci for Omsk haemorrhagic fever virus is favoured by a combination of landscape, climatic, and biotic factors. The landscape in the foci identified so far consists of forested areas, to some degree, and steppe with multiple marshes and lakes. The Novosibirsk region contains more than 3000 irregularly distributed lakes occupying 5000 km². The territory exhibits altitudes of 150–200 m above sea level. The climate is continental with a long winter (up to 5 months) and a short, hot, wet summer. Most rainfall is recorded in summer (June to September).[18] Two types of so-called natural pseudofoci are currently recognised in western Siberia: active, in which about 35% of inhabitants, including young children, are seropositive, and potential, which are characterised by low (<15%) seroprevalence and no seropositive children younger than 14 years.[22,23]

Human beings can be infected with Omsk haemorrhagic fever virus by transmissive (via a feeding infected tick) or non-transmissive (respiratory and probably alimentary) routes. Person-to-person transmission does not seem to occur, and no within-hospital or within-family outbreaks have been seen, with the exception of multiple family members involved in hunting muskrats and the removal and treatment of their skins.[24] In forest-steppe areas of Siberia, the principal vector and reservoir of Omsk haemorrhagic fever virus is the tick *D reticulatus*; in the steppe regions of southern and western Siberia, the virus is transmitted mainly by the tick *D marginatus*.[25,26] Gamasid mites and the taiga tick (*Ixodes persulcatus*) are believed to be involved in the sylvatic cycle of Omsk haemorrhagic fever virus.[27] The virus has also been successfully isolated from mosquitoes (*Aedes excrucians*, *Mansonia richiardii*, and *A flavescens*),[28] but their role as vectors is very minor, if any.[18] Omsk haemorrhagic fever virus has been trans-stadially and transovarially transmitted in *D reticulatus* ticks under experimental conditions.[29]

The virus is almost certainly maintained in the tick population by being delivered from infected to non-infected ticks when they both feed at the same site of skin on a vertebrate host.[13,30,31] *D reticulatus* lives as a parasite on more than 37 different mammal and bird species in Siberia. Tick larvae feed on small mammals during June and July, turn into nymphs that feed during July and August, and moult into adults in the Autumn (September to October), which feed on wild ungulates and human beings. Immature forms in forest-steppe habitats in particular feed on narrow-skulled voles (*Microtus gregalis*),[32] which have cyclical population expansions and decreases; the expansion of the virus-infected tick population coincides

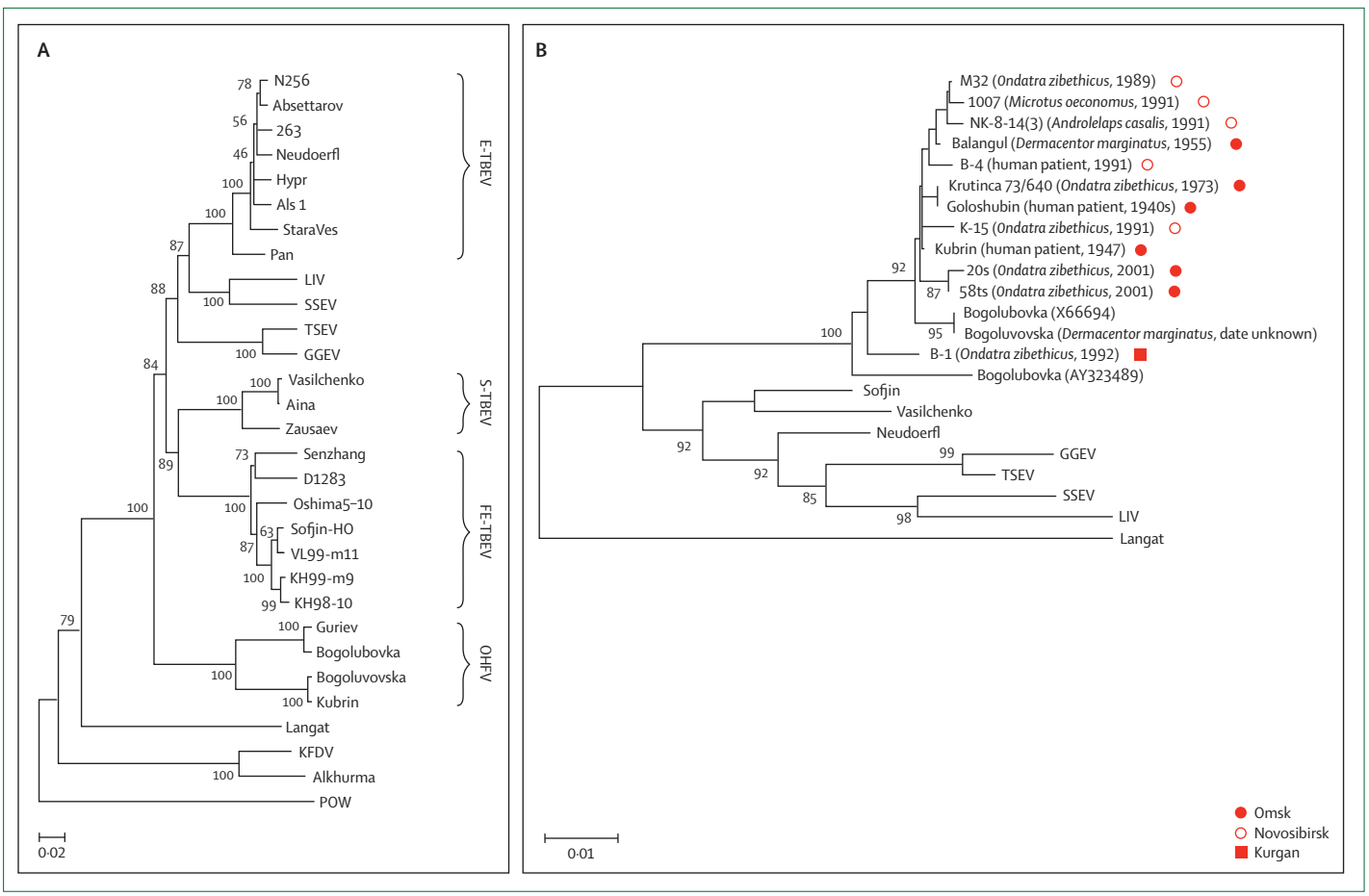

Figure 3: **Phylogenetic trees for Omsk haemorrhagic fever virus**

(A) Genetic relation of Omsk haemorrhagic fever virus to other selected tick-borne flaviviruses, according to complete nucleotide sequences of E protein gene. (B) Complete deduced aminoacid sequence of E protein illustrating the relations of early and late strains of Omsk haemorrhagic fever virus from different origins and different localities. E-TBEV-European subtype of TBEV. FE-TBEV=Far Eastern subtype of TBEV. GGEV=Greek goat encephalitis virus. KFDV=Kyasanur forest disease virus. LIV=louping ill virus. OHFV=Omsk haemorrhagic fever virus. POW=Powassan virus. SSEV=Spanish sheep encephalitis virus. S-TBEV=Siberian subtype of TBEV. TBEV=tick-borne encephalitis virus. TSEV=Turkish sheep encephalitis virus.

with increases in vole populations.[33] The distribution of infected ticks is irregular across foci.[25,34] Agricultural workers and collectors of mushrooms or wild berries in the focal areas are at the highest risk of infection by ticks carrying Omsk haemorrhagic fever virus. Ticks can also be transmitted to people by dogs.[24] Since the 1960s, the density and infectivity of *D reticulatus* and its main host, the narrow-skulled vole, has decreased, which is believed to be the reason for substantial decreases in the prevalence of Omsk haemorrhagic fever.[22]

D marginatus is frequently found on human beings in western Siberia.[32] In 1971–89, the narrow-skulled vole population notably decreased owing to human-mediated changes to forest-steppe landscapes.[35] The sizes of areas inhabited by ticks were also seen to decrease.

In the period before activation of natural foci of Omsk haemorrhagic fever virus in 1999–2000, marked by emergence or re-emergence of epidemic activity, the fauna of northern forest-steppe had changed, leading to the northern border of *D marginatus* habitats moving to the south and the population of *I persulcatus* ticks in forest ecotopes and ecotones overtaking that of *D reticulatus*.[36] The population density of *D reticulatus* ticks, however, remained similar to that in the period 1946–50.

At the time of discovery of Omsk haemorrhagic fever virus, the proportion of infected ticks did not exceed 2%.[37,38] In the same foci at that time, the proportion of ticks positive for tick-borne encephalitis virus was 0·6–1·8%. By contrast, at the present time ixodid ticks are generally negative for Omsk haemorrhagic fever virus, whereas 17·2% of *D reticulatus* and 1·8–15·3% of *I persulcatus* ticks are infected with tick-borne encephalitis virus.[36] This change could be a consequence of Siberian strains being replaced with more virulent Far Eastern strains changes in the natural foci of western Siberia.[39] Alternatively, Omsk haemorrhagic fever virus is still present in small vertebrates, and there are even mixed infections with tick-borne encephalitis virus.[40] The existence of mixed infections suggests (but does not rule

out) a lack of viral interference between the two viruses. Mixed infections are thought to be frequent, on the basis of many isolates of Omsk haemorrhagic fever virus and tick-borne encephalitis virus from vertebrates and arthropods being difficult to distinguish by classic virological methods (neutralisation test, complement binding assay, haemagglutination inhibiton test, and diffuse agar precipitation).[40] Modern PCR-based methods should provide more-detailed insight.

Non-transmissive infection with Omsk haemorrhagic fever virus occurs mainly after close contact with infected muskrats. The patients are generally rural residents, agricultural workers, and people involved in hunting and skinning these animals.[24] Hunters frequently destroy muskrats' homes and seize the rodents with bare hands, which represents a high-risk activity.[1]

Seroepidemiological data show that many animal species are in contact with Omsk haemorrhagic fever virus, including rodents, insectivores, birds, ungulates, and domestic animals. Some wild hosts develop latent chronic infections and others develop acute, and in some cases fatal, infections (panel 1). Therefore, natural foci for Omsk haemorrhagic fever virus involve multiple hosts, especially water voles (*Arvicola amphibius*) and narrow-skulled voles.[18,41]

Muskrats are very sensitive and susceptible to Omsk haemorrhagic fever virus and the infection is frequently fatal in this species.[25] The animals develop haemorrhagic disease with high viraemia and fever that can last 3 weeks or longer. Virus is shed in urine, faeces and blood. Experimental infection of other species native to Siberia has shown that only Norway rats are as sensitive to Omsk haemorrhagic fever virus; white, wild, and cotton rats, rabbits and dogs are not susceptible; hedgehogs are susceptible and develop acute disease and monkeys, sheep, lambs, calves, and piglets are susceptible but generally develop asymptomatic infection (panel 1).[18] Omsk haemorrhagic fever virus survives for about 3 days in goats, and can pass from the blood into the mammary gland and be found in milk for several days.[24] However, no milk-borne outbreaks of Omsk haemorrhagic fever have been reported.

Omsk haemorrhagic fever virus survives in lake water for at least 2 weeks in the Summer (June and July) and for 3·5 months in the Winter (January onwards). Saturation of water with zooplankton, phytoplankton, and other organisms lengthens virus survival. Water animals and those living near water may, therefore, become infected via lake water contaminated with Omsk haemorrhagic fever virus from muskrat corpses, urine, or faeces. Detailed data on this mode of transmission are, however, not available.[18]

***Panel 1:* Clinical course of Omsk haemorrhagic fever after experimental extraneural inoculation in wild vertebrates[18]**

Asymptomatic disease with viraemia

- Norway rat (brown rat; *Rattus norvegicus*)
- Water vole (*Arvicola terrestris*)
- Striped field mouse (*Apodemus agrarius*)
- Field vole (*Microtus agrestis*)
- Harvest mouse (*Micromys minutus*)
- Northern redbacked vole (*Clethrionomys rutilus*)
- Steppe lemming (*Lagurus lagurus*)
- Striped hairy-footed hamster (*Phodopus sungorus*)
- Northern birch mose (*Sicista betulina*)
- Steppe polecat (*Mustela eversmanni*)
- Common hamster (*Cricetus cricetus*)
- Ground frog (*Rana terrestris*)
- Pochard (*Aythya ferina*)
- Pintail (*Anas acuta*)
- Common kestrel (*Falco tinnunculus*)
- Red-footed falcon (*Falco vespertinus*)
- Marsh harrier (*Circus aeruginosus*)
- Black-headed gull (*Chroicocephalus ridibundus*)

Acute disease in some animals, latent disease in others

- Root vole (*Microtus oeconomus*)
- Narrow-skulled vole (*Microtus gregalis*)
- Red-cheeked suslik (*Citellus erythrogenys*)
- Spotted suslik (*Spermophilus suslicus*)
- Hedgehog
- Weasel (*Mustela spp*)

Acute neuroinfection with death

- Muskrat (*Ondatra zibethicus*)

Epidemiology

Morbidity from Omsk haemorrhagic fever in human beings has two seasonal peaks that correlate with activity of *D reticulatus* in the northern forest-steppe regions and with that of *D marginatus* in the southern and western areas of Siberia. The first cases generally occur in April (1% of the annual total number of cases), with incidence reaching its height in May and June (73% of total cases). Incidence declines in July. A second phase of morbidity occurs in August to September (21%). Outbreaks of Omsk haemorrhagic fever that arise in people who have been in contact with muskrats generally occur in the Autumn or Winter (August to December), which correlates with the muskrat hunting season.[1] For example, in 1988–92, 83·3% of all Omsk haemorrhagic fever infections were registered in September to October (figure 4).[42]

Between 1946 and 1958, 972 cases of Omsk haemorrhagic fever were officially recorded. The incidence is, however, assumed to have been much higher because mild cases were not likely to have all been recorded.[23] The incidence of Omsk haemorrhagic fever was the highest among people aged 20–40 years. Infections in children younger than 15 years comprised around a third of all cases. In 1960–70, the incidence decreased remarkably. The size and number of foci were, therefore, thought to be declining. In the past 20 years, the disease has only been reported in the Novosibirsk region. In 1988, three cases were officially recorded, all in muskrat hunters in western Siberia. In

1989, infections in 22 patients were recorded. The largest outbreaks since 1970 were in 1990 (29 cases) and 1991 (38 cases).[42] From a total of 165 cases of Omsk haemorrhagic fever reported in 1988–97, ten were associated with tick bites and 155 were in muskrat hunters and poachers.[23] From the seven cases reported in 1998, one was fatal and three were severe.[43] The correct numbers of infections each year, however, remain unclear because mild cases of Omsk haemorrhagic fever are frequently misdiagnosed or are still not reported.

Clinical signs and symptoms

A detailed description of the clinical signs and symptoms of Omsk haemorrhagic fever has been derived from human morbidity studies done during outbreaks in 1945–48 in the Omsk region[2,44–47] and in 1988–92 in the Novosibirsk region (panel 2).[42] Accidental laboratory infections with Omsk haemorrhagic fever virus are also well documented.[48,49]

The incubation period of Omsk haemorrhagic fever lasts on average 3–7 days, sometimes with prodromal manifestations, such as malaise, aches, and pains. A high continuous fever of 39–40°C is seen in all cases, and other frequent symptoms are headache, cough, muscle pain, gastrointestinal symptoms, dehydration, and bleeding from the nose, mouth, and uterus, with skin haemorrhages. Fever is likely to be accompanied by chill that lasts 8–15 days. Various characteristic clinical signs have been reported at disease onset: arterial hypotension and bradycardia, hyperaemia of the face, neck, and breast, acute scleral injection, bright colourisation and light oedema of the tunica mucosa in the mouth and throat, unusual dryness of mucous membranes, especially on the tongue, bleeding from the nose, mouth, or both on one or more occasions, a putrid odour from the mouth, and, most prominently, an enlarged liver. These signs, especially hyperaemia (in particular affecting the pharynx) and scleral injection, worsen over the first 3–4 days of clinical disease.[42] In addition, the face becomes slightly puffy and labial fissures and crusts appear.

Moderate albuminuria, cylindruria, and intermittent haematuria begin on days 5–8 and disappear around days 15–25. Patients frequently complain of pain in the lower-leg joints and calf muscles. In many cases, continuous gingivitis without pronounced stomatorrhagia, hyperaemia of the soft palate and tonsils, and uvular oedema (but without inflammatory changes) are seen. Rarely, surface necroses of the pharynx are present. Skin hyperaesthesia and muscle pain are recorded in most cases, followed quickly by increased intensity of haemorrhagic signs, in particular bleeding in the mouth, uterus, skin, and mucosa, and in serious cases gastrointestinal and pulmonary bleeding. Petechial rash on the skin of the abdomen and upper and lower extremities has been noted with increasing frequency since the outbreaks in 1988–92, being reported in up to 22% of cases; in a few cases a typhoid-like maculopapular rash has been seen.[44]

Panel 2: **Clinical signs and symptoms of Omsk haemorrhagic fever in human beings[3]**

Haematology
- High haemoglobin concentrations at disease onset
- Leucopenia with left shift
- Initial normal or decreased ESR that later accelerates
- Neutrophilia with left shift
- Monocytosis
- Thrombocytopenia

Blood biochemistry
- Hypoproteinaemia and moderate uraemia at disease peak
- Serum bilirubin, cholesterol, and calcium concentrations unchanged
- Decrease in complement titre

Cardiovascular system
- Diffuse or focal dystrophic degenerative changes of myocardium
- Dilatation of heart margin (mainly in the left ventricle)
- Deaf tones
- Severe arterial hypotonia
- Hyperaemia of face and upper trunk
- Injection of scleral vessels
- Exanthema
- Scant petechial rash
- Nasal, pulmonary, gastrointestinal, uterine and other haemorrhages

Pulmonary*
- Bronchitis
- Atypical pneumonia (absence of cough, small amount of sputum, no pain in thorax, no inflammation of the pleura)

Renal
- Moderate albuminuria
- Cylinduria
- Intermittent haematuria

Nervous system
- Headache, muscle pain, etc
- Kernig's sign (23% of cases)
- Occipital rigidity (40% of cases)
- Lasegne's sign (20% of cases)
- Loss of taste
- Decrease in hearing
- Acute adynamia
- Behavioural and psychological difficulties

*Affected in a third of cases.

After 1–2 weeks of symptomatic disease, 50–70% of patients recover without any complications; a second phase of disease, starting at the beginning of the third week of clinical illness, is seen in 30–50% of cases. This stage lasts 5–14 days and is characterised by continued high fever, reappearance of the primary symptoms (nausea, chill, reddening of the face, scleral injection,

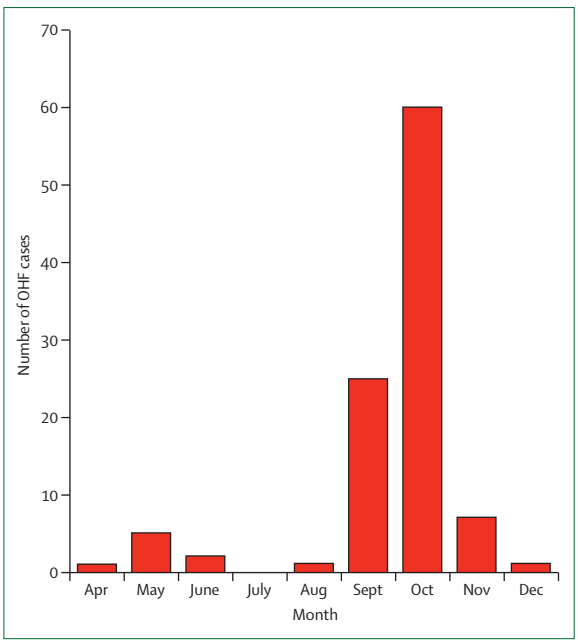

Figure 4: **Seasonal variability in Omsk haemorrhagic fever morbidity in years 1988–92 in the Novosibirsk region**
83·3% of all cases were registered in September to October, which corresponds with the muskrat hunting season.[40] OHF=Omsk haemorrhagic fever.

nasal, gingival, and uterine bleeding, and haematuria), and new encephalitic symptoms (continuous headache and meningism). Petechial rash reappears in some patients. Bruises appear at sites of pressure or injection. Blood analysis shows leucopenia, thrombocytopenia, and plasmacytosis. Internal organs are frequently affected, especially the lungs and kidneys; bronchitis, pneumonia, or both are found in a third of cases. The symptoms of diffuse encephalitis generally disappear along with other second-phase symptoms. Chronic forms of Omsk haemorrhagic fever have not been reported in human beings. In children meningism has been reported in 41% of cases; paresis has also occasionally been recorded.[48]

Accidental laboratory infections of Omsk haemorrhagic fever after needle injury or inspiration of a contaminated aerosol have occurred in Russia and Czechoslovakia.[48,49] The clinical course of such infections has generally been similar to that in disease occurring naturally, although in some cases the course has been more severe. This difference is explained by a higher virulence of the strains used in laboratory studies than that of naturally occurring strains, and high inoculation doses. From the 21 cases of laboratory infections reported in Russia, seven (31%) exhibited two-phase disease; leucopenia with left shift, thrombocytopenia, and changes in mouth mucosa were seen in all 21 patients, haemorrhagic syndrome in 13, respiratory tract involvement in eight, kidney involvement in five, heart involvement in seven, and mild neurological symptoms in six.[48] In Czechoslovakia, one patient developed meningoencephalitis followed by a severe depressive syndrome, but no haemorrhagic signs or pathology were seen in the kidneys, respiratory tract, or heart.[48] Another patient from Czechoslovakia developed mild haemorrhagic disease and made a complete recovery.[49]

Recovery and complications

Disease prognosis is generally favourable. Complete recovery is typical, albeit after a long period of asthenia.[3] Rarely, patients develop permanent complications, which include weakness, hearing loss, hair loss, and behavioural and psychological difficulties associated with neurological conditions (poor memory, impaired ability to concentrate or work, etc). A long convalescent period is important to lessen the risk of permanent complications.[49]

Reported mortality ranges from 0·4% to 2·5%.[47] In fatal cases, the patients die after rapid onset of haemorrhagic signs or at a later stage, as a result of septic complication (suppurative bilateral parotidis or empyema).[47]

Not all cases of Omsk haemorrhagic fever are severe. During the outbreak in 1945–46, up to 18% of cases were confirmed to be mild. These patients were not febrile, had only generalised symptoms related to infection, and had no abnormal haematological features. In a later outbreak (1988–89), more than 80% of patients had mild forms of the disease without haemorrhagic symptoms, and mortality was reported to be about 1%.[42]

Pathogenesis

Very little is known about the pathogenesis of Omsk haemorrhagic fever in human beings. The underlying molecular mechanism remains undefined. The virus is pantropic, but has a marked affinity to haemopoetic and vascular tissues. Haemosiderin deposits are present in the Kupffer cells of the liver. Effects on the involuntary nervous system and vascular system cause the most important clinical manifestations. Pathological changes in brain parenchyma that might be associated with effects on the involuntary nervous system include haemorrhages, focal proliferation of glial elements in the brain, and sometimes perivascular inflammatory infiltrates.[46] Oedema in the brain causes the sensory changes. Hypotonia can lead to a collapse and shock in severe cases, especially early in the clinical disease course.[24] Sensitivity to other infections is increased, in particular to those caused by purulent bacteria.[46]

Investigations into the pathogenesis of Omsk haemorrhagic fever have been done, mostly in laboratory mice and non-human primates. Laboratory mice are sensitive to infection after extraneural or intracerebral inoculation, and develop fatal neuroinfection. Clinical signs include spasms, paresis, and paralysis. The infected animals are weakened, with poor mobility and appetite, apathy, and hyperpnoea. Most of the virus is accumulated in the cerebellum and brain hemispheres. Smaller titres, all of similar concentrations, are found in lungs, kidney, blood, and faeces. The lowest titres are in the spleen and liver.[50] In subcutaneously inoculated mice the

pathogenetic process is characterised by the initial viral replication in subcutaneous tissues, induction of viraemia, and invasion of the internal organs. Finally, the virus crosses the blood–brain barrier and enters the brain.[50] Omsk haemorrhagic fever virus infection in juvenile mice induces high interferon production in brain tissue.[51] Mice infected intranasally develop pneumonia associated with weakness, prostration, and paralysis of extremities.[2]

In another study, mice infected with Omsk haemorrhagic fever virus developed meningoencephalitis with the accumulation of viral antigen predominantly in the cerebellum, but did not develop neurological symptoms. In addition, the mice had substantially enlarged spleens, some indications of pathology in the kidney, liver, or both, and gastrointestinal haemorrhage.[52,53]

In experimentally infected macaques (*Macaca radiata*) no signs of clinical disease developed, no virus could be isolated from tissues or blood, and no clinically important histological lesions were found. Serum aminotransferase concentrations were transiently elevated and seroconversion was clearly identified, which indicate that viral replication occurred.[54]

Diagnosis

Diagnosis of Omsk haemorrhagic fever is frequently based only on clinical and epidemiological observations, but serological tests are crucial for a reliable and accurate diagnosis. Differential diagnosis should take into account pseudotuberculosis, typhus, leptospirosis, brucellosis, rickettsiosis, and so on. Antibodies to Omsk haemorrhagic fever virus can be detected in serum samples by ELISA. Seroconversion with paired sera is examined with haemagglutination-inhibition,[55] complement-fixation, and neutralisation[56] tests.

ELISA is most effective when antibody titres are measured in serum samples drawn during the first week of illness and 2–3 weeks later. Haemagglutination antibody titres rise rapidly within the first week of illness and are long-lived. The complement fixation test has moderate specificity, but does not have good sensitivity and, therefore, should not be used alone. A fourfold change is interpreted as indicating infection within the previous 1–3 weeks, but the timing might be longer, for example in elderly patients. The neutralisation test is deemed to be the most specific for identification of arbovirus infections. Neutralising antibodies generally become detectable within 1 week of the onset of disease and persist for years and possibly lifelong in human beings. Of note, however, antibodies to other tick-borne flaviviruses (mainly to tick-borne encephalitis virus) also have the ability to cross-neutralise Omsk haemorrhagic fever virus.[57–59]

Several reverse-transcription or real-time reverse-transcription PCR protocols for the universal detection and identification of flaviviruses, including Omsk haemorrhagic fever virus, have been published.[60,61] These methods, however, have not yet been assessed specifically in the diagnosis of Omsk haemorrhagic fever. On the basis of reported data, the Omsk haemorrhagic fever virus seems to be present in blood during the first phase of the disease, but not during the second.[46] Since the first phase is associated with non-specific mild symptoms, patients most frequently seek medical advice during the second phase, when molecular detection of the virus in serum is likely to be unsuccessful. This situation correlates with that for human tick-borne encephalitis.[62] Despite advances in molecular detection of flaviviruses in clinical samples, therefore, serological testing remains the gold standard approach in the diagnosis of Omsk haemorrhagic fever in human beings. The reverse-transcription PCR methods seem to be more suitable for screening ticks and reservoir animals for Omsk haemorrhagic fever virus, or for the investigation of post-mortem samples.

Omsk haemorrhagic fever virus can be isolated from blood samples collected only in the first days of the disease. The virus is isolated by inoculation into cultures of several cell lines and in suckling mice aged 2–4 days. Reported data indicate that isolation of the virus in the second phase of the disease has never been successful.[48] Omsk haemorrhagic fever virus is classified as a Biosafety Level 4 agent in several countries[63] and, therefore, only a few diagnostic laboratories in the world can isolate and characterise the virus. Post-mortem tissues can be used for virus isolation or investigation by immunofluorescence, electron microscopy or reverse-transcription PCR. All potential sources of exposure (needles, blades, instruments, etc) must be handled with extreme care.[64]

Therapy and prevention

No treatments with specific effects against Omsk haemorrhagic fever virus are known, and those used currently are only applied to control symptoms. The main focus of therapy is to keep haemorrhagic and other complications to a minimum. The disease is generally self-limiting, but patients must be prescribed strict bed rest. General measures include early admission to hospital, careful nursing, and an abundant intake of liquids.[3] A nutritious diet, administration of chloride potassium and glucose, vitamins K and C, and a long convalescence period are recommended.[65] Any complications (pneumonia, heart insufficiency, bacterial infections, etc) should be treated. Aspirin and non-steroidal anti-inflammatory drugs should be avoided.[3]

Several drugs against Omsk haemorrhagic fever virus have been tested in cell culture and laboratory animal studies. Screening tests showed that high concentrations of ribavirin or the interferon inducers larifan and rifastin moderately suppressed viral reproduction, and recombinant human interferon α-2b completely inhibited viral reproduction in cell culture. Larifan demonstrated the highest antiviral efficacy against Omsk haemorrhagic fever virus in laboratory animals. This drug prevented

the death of 65% infected mice and substantially lessened disease severity in rabbits.[66] No data from clinical studies in human beings are, however, available.

As early as in 1948, Chumakov[2] had developed a formalin-inactivated vaccine derived from the brain tissue of artificially infected mice. This vaccine exhibited good protection against Omsk haemorrhagic fever virus in experimental and human studies; however, the production was discontinued owing to adverse reactions to the mouse-brain components in the vaccine.[67] On the basis of the antigenic similarity of Omsk haemorrhagic fever virus and tick-borne encephalitis virus, vaccines to the latter were used as a preventive measure against infection with Omsk haemorrhagic fever virus during the 1991 outbreak. Its use was, however, permitted under a special directive by the local government; no official policy exists for this use, and no experimental data support the efficacy of this approach.

Conclusion

Given the lack of a specific treatment or vaccine against Omsk haemorrhagic fever virus, elimination of wild rodents (especially water voles and other small mammals in muskrat basins) and their ectoparasites as reservoirs for Omsk haemorrhagic fever virus is a basic approach to sanitising natural foci. Preventive measures against potentially infected blood-sucking arthropods are of particular importance. People entering areas known to be natural foci should protect themselves from tick bites by dressing appropriately. Workers in the focal areas should wear especially designed nylon protective clothes.[24] Application of insect repellents is also beneficial; those containing N,N-diethylmetatoluamide can be applied directly on the skin. Compounds containing permethrin have an acaricidal and repellent effect and should be used on clothing and camping equipment. People should avoid any contact with muskrats, especially sick muskrats. Drinking of non-pasteurized goat milk should also be avoided in the risk areas. Fishermen, shepherds, hunters, and other workers on farming enterprises represent high-risk groups for Omsk haemorrhagic fever.[24]

Contributors

All authors searched for relevant articles. DR wrote the manuscript, which was edited by the other authors. VVY, SET, and LSK contributed substantially to the ecology and epidemiology section, and SET to the clinical manifestation section. VVY prepared figure 2 and LSK provided data for figure 3. All authors saw and approved the final draft of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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