Accepted: 14 April 2018

DOI: 10.1111/jmp.12351

REVIEW ARTICLE

WILEY

Monkey viral pathology in the Sukhum colony and modeling human viral infections

Boris A. Lapin[1] | **Zinaida V. Shevtsova**[2]

[1]Research Institute of Medical Primatology, Sochi, Russia

[2]Research Institute of Experimental Pathology and Therapy of the Abkhazian Academy of Sciences, Sukhum, Abkhazia

Correspondence
Boris A. Lapin, Research Institute of Medical Primatology, Sochi, Russia.
Email: blapin@yandex.ru

Abstract

The data characterizing spontaneous infections of Old World monkeys: measles, poliomyelitis, hepatitis A (HPA), encephalomyocarditis, coronavirus infection, simian hemorrhagic fever (SHF), are presented. The experimental infections were reproduced with the isolated pathogens. On these models, pathogenesis and epidemiology of these diseases were studied. The efficiency of poliomyelitis, measles and HPA vaccines is shown. The priority of data on the discovery of earlier unknown disease—SHF and "Sukhumi" virus—are emphasized. Several important pathogenic mechanisms common for various hemorrhagic fevers were studied on experimental SHF of macaques. This model is uniquely safe and adequate for the assessment of therapy of hemorrhagic fevers dangerous for humans.

KEYWORDS

encephalomyocarditis, hepatitis A, measles, poliomyelitis, simian hemorrhagic fever

1 | INTRODUCTION

In this article, results of long-term comparative research of primate viral infections of monkeys and humans are presented. These data are interesting for the characterization of monkeys as an object in medical-biological research. Also, they are important for preventing epizooty and infection of personnel contacting with monkeys in a monkey colony. The characterization of spontaneous infections in monkeys is very important for further use of monkeys as models of analogous human infections. The similar to human manifestations of the most part of these infections can be reproduced in monkeys that is explained by evolutionary established similarity of main physiological systems of monkeys and humans. The evolutional similarity of infectious agents, seemingly duplicates of human viruses, should be also taken into account. The contribution made by monkeys to research of human virus pathology is invaluable. The use of these laboratory primates helped to prove etiology of the most part of viral infections, to study their pathogenesis and epidemiology, and to develop the preventive care.

The care and use of the monkeys are carried out in accordance with the rules of the humane care of animals in Russia (and in USSR) and with approved experimental protocols.

Studies of viral pathology were started at Sukhum Medical-Biological Station of the USSR Academy of Medical Sciences in 1950s. Research of spontaneous and experimental poliomyelitis was performed under the guidance of academicians M.P. Chumakov and M.K. Voroshilova, measles—under the leadership of academician P.G. Sergiev.

Continuous virological research began at the Sukhum Institute in 1960s. Serological screening of 7 monkey species (more than 1000 animals) revealed antibodies to wide spectrum of viruses: measles, flu, parainfluenza, adeno-, rota-, entero-, corona-, and herpes. Infection with these viruses usually was inapparent. However, in a number of cases, activation of latent infections and also epizooties were observed. It happened because of weakening immunodefense (capture, acclimatization stress, radiation exposure).

2 | SPONTANEOUS INFECTIONS

Short information on spontaneous viral infections of various monkey species studied in the Sukhum colony is presented in Table 1. Each infection proceeded with corresponding clinical and pathological

TABLE 1 Spontaneous viral infections of monkeys

Nosological diagnosis	Years	Monkey species	Isolated viruses	Family
Measles[1,2]	1954, 1962	Rhesus macaques, hamadryas baboons, Assam macaques	Human measles virus	Paramyxoviridae
Poliomyelitis[2,3]	1957	Rhesus macaques	Human poliovirus	Picornaviridae
Simian hemorrhagic fever[4-15]	1964, 1967, 1974	Rhesus macaques, pig-tailed macaques, patas monkeys	SHV strain "Sukhumi-64"	Arteriviridae
Encephalomyocarditis[16-18]	1970, 1978	Rhesus macaques, hamadryas baboons	Encephalomyocarditis virus, strain EMC-70	Picornaviridae
Conjunctivitis pneumonia[19]	1972, 1973	Rhesus macaques, hamadryas baboons	Monkey adenovirus SV-14	Adenoviridae
Ulcerative stomatitis[20]	1974	Rhesus macaques	Monkey herpes B virus	Herpesviridae
Polio-like enteroviral disease[21]	1981-1982	Rhesus macaques	Monkey enterovirus SV-49	Picornaviridae
Pneumonia and/or enterocolitis[22]	1982-1986	Rhesus macaques, hamadryas baboons	Monkey coronaviruses, strains CVMR and CVPH	Coronaviridae
Hepatitis A[23-25]	1985-1992	Cynomolgus monkeys, bear macaques, rhesus macaques, green monkeys, hamadryas baboons	Hepatitis A virus, strains VHA-MR, VHA-GM, VHA-PH	Picornaviridae

signs. Infectious agents were identified. Some of them were identical to human viruses; others were simian viruses.

2.1 | Measles

In 1954, measles outbreak occurred in the Sukhumi colony. Infection spread among monkeys kept in the same building. In rhesus macaques and hamadryas baboons, the clinically apparent disease progressed. It was characterized by catarrhal signs and rash abundant. In cynomolgus and green monkeys, infection was inapparent.[1] The second measles outbreak took place in 1962 among Assam macaques, which were in experiment with small doses of gamma rays during a year. The disease was severe, with characteristic complications and death.[2]

2.2 | Poliomyelitis

In 1957, in the Sukhumi colony in rhesus macaques polio outbreak spontaneously arose. Clinical manifestations and pathomorphological changes specific for polio were registered.[3] The main manifestations were paralyses of lower and upper extremities and respiratory muscles. A morphological study indicated a massive loss of anterior horn cells of the spinal cord in cervical and lumbar enlargements. Type 2 poliovirus was isolated from the brain of perished monkeys.

2.3 | Simian hemorrhagic fever (SHF)

In 1964, an enzooty of new unknown disease occurred. This disease was called by us SHF. In a month, 55 rhesus macaques imported from India died. Main manifestations of the infection were hemorrhagic diathesis and damage of neurological status.[4-6] Clinical signs were also fever, apathy, anorexia, tremor, ataxia, limb weakness (rarely, pareses). There was an increase in tendon reflexes and muscular tone. Most animals had petechial skin rash, more rarely - nosebleed and intestinal bleeding. In the terminal period, temperature and blood pressure drastically decreased. Monkeys died in 8-12 days. Disorder of blood circulation in the microcirculatory bloodstream, hemorrhagic diathesis in the central nervous system, diffuse encephalomyelitis, widespread destruction of lymphoid elements and focal coagulative necroses in parenchymatous organs were histologically observed. From the blood and brain, a filterable agent was isolated.[6,7] The virus differed from known causative agents of hemorrhagic fevers. He was apathogenic for small laboratory animals, did not possess hemagglutinating properties, and did not reproduce itself in any of 39 cell cultures. Only rhesus macaque embryonic kidney cells (PEMR) were permissive. Immunotyping showed that it was the new virus different from ones known earlier.[6,7] Virus strain discovered by Z.V. Shevtsova in 1964 and designated as "Sukhumi-64" was registered at the State collection of viruses of the USSR Ministry of Public Health. The certificate was signed by Dr. V.M. Zhdanov, the member of International committee on taxonomy and classification of viruses. Two years later after our first communications,[4,5] American scientists reported that an enzooty of similar disease took place in the NIH rhesus macaque colony in Bethesda at the end of 1964.[8] The isolated virus strain was designated as *Bethesda 64*.[9] After exchange of virus strains between USSR and United States, it was found that viruses were antigenically similar but not identical.[10,11] Another 2 outbreaks were observed in the Sukhumi colony in 1967 and 1974. The infection source was African patas monkeys carrying latent infection and located in the same room as Asian macaques. SHF was the serious problem of primatological centers: 17 enzooties were registered by 1996.[12] In some colonies, a number of died macaques was from 200 to 500.[13] Later, SHV-related variants were isolated from African monkeys of various species from wild animals as well as from those habitating in National parks. Today, 12 isolates are studied in detail by American and Russian virologists. All of them

are arteriviruses, but differ by their genome structures and homology. The strain "Sukhumi-64" was included in genus Arteriviruses as *Sukhumi simarterivirus species* called *simian hemorrhagic encephalitis virus (SHEV).* GenBank, USA, assigned own number to SHEV.[14]

2.4 | Encephalomyocarditis

Group illness of encephalomyocarditis was registered twice in the Sukhum colony: among macaques in 1970 and hamadryas baboon in 1978. The disease proceeded with brain and myocardium damage and was lethal in a number of cases.[15,16] The encephalomyocarditis virus isolated from dead monkeys and designated as EMC-70 was identical to the prototypical strain EMC-Paris.[16] This infection is still the serious problem of colonies and zoos because of many fatal outbreaks from 1980 to 2005.[17,18] Human illness is known only from outbreaks among recruits.

2.5 | Adenovirus

From 1972 to 1973 year, there have been cases of acute conjunctivitis sometimes accompanied by pneumonia. From the conjunctive content of diseased animals was isolated a virus cytopathic for a number of cell cultures.[19] Biological, physico-chemical, and electron-microscopic analyses showed that it was simian adenovirus SV-37.

2.6 | Herpesvirus

The group of rhesus macaques underwent radiation sickness and lapsed into ulcerative stomatitis. The simian herpes virus B was isolated from diseased sites.[20]

2.7 | Enterovirus

In 1982, the infection was spread among rhesus macaques. It was clinically characterized by the disorder of lower limb locomotor activity and the development of atrophy and contractures. Histologically observed myositis with lysis of limb muscle fibers and inflammation of brown fat were found. The loss of neurons was detected in lumbar segments of the spinal cord. From diseased monkeys, the SV-49 virus was isolated.[21]

2.8 | Coronavirus

We also described spontaneous coronavirus infection in rhesus macaques and hamadryas baboons. It was persistent with periodical recrudescences including pneumonia and (or) enterocolitis.[22] A morphological study revealed diffuse lymphocytic and macrophage infiltration of the intestine mucosa. In the lungs, changes in characteristic of pneumonia (the presence of giant cells, signs of carnification) were determined. Coronaviruses were found in bowel, pancreas, and lungs of perished monkeys. Strains were designated as CVMR and CVPH and registered at the State collection of viruses.

2.9 | Hepatitis A

In contrary to existent opinion, we found the natural sensitivity of Old World monkeys to hepatitis A virus (HAV). Epizooties of this infection in 4 monkey species imported from natural habitats were studied and described by us.[23,24] Strains isolated from diseased monkeys were not antigenically different from human HAV.[25]

3 | EXPERIMENTAL INFECTIONS AND MODEL DEVELOPMENT

The second part of our article is dedicated to modeling 6 above-described infections in monkeys (Table 2).

3.1 | Poliomyelitis

Experimental poliomyelitis was induced in 4 monkey species. In animals infected by human poliovirus, paralyses of lower limbs and characteristic pathomorphological changes in cells of ventral horns of the spinal cord were observed.[26] Problems of polio pathogenesis

TABLE 2 Models of viral infections

Infection	Used virus	Monkey species	Studied
Poliomyelitis[26]	Human poliovirus	Rhesus macaques, cynomolgus monkeys, green monkeys, hamadryas baboons	Pathogenesis, epidemiology, testing vaccine strains
Measles[27]	Human measles virus	Rhesus macaques, hamadryas baboons	Pathogenesis, vaccinal process, testing vaccine strains
Coronavirus infection[28]	Coronavirus of rhesus macaques	Rhesus macaques	Clinical and pathomorphological characterization
Encephalomyocarditis[29,30]	Encephalomyocarditis virus EMC-70	Rhesus macaques, hamadryas baboons, green monkeys, patas monkeys	Clinical and pathomorphological characterization
Hepatitis A[31,32]	Human hepatitis A virus	Rhesus macaques	Clinical and pathomorphological characterization, testing vaccine
Simian hemorrhagic fever[13,33,34]	SHV "Sukhumi- 64"	Rhesus macaques	Clinical and pathomorphological characterization, thanatogenesis

and epidemiology were studied with these models, and immunogenicity of live-attenuated virus was shown. Obtained data allowed to develop successful prophylaxis of poliomyelitis.

3.2 | Measles

Inoculation of 3 monkey species by material from children suffering from measles played an important role in study and prophylaxis of measles. Virological and histological research revealed main pathogenic mechanisms and the role of systemic change of reticuloendothelium and lymphoid tissue. Comparative research performed in monkeys gave data on pathogenesis of experimental measles and vaccinal process developed after introduction of live-attenuated vaccine L-4 (Leningrad-4) used in measles preventive care.[27]

3.3 | Coronavirus

Experimental coronavirus infection of rhesus macaques and hamadryas baboons was performed using the strains isolated from diseased monkeys and antigenically related to human coronavirus OS-43. Infection similar to spontaneous was persistent with the latent course and periodical recrudescences including pneumonia and (or) enterocolitis.[28] Actuality of our model is defined by an increasing role of coronaviruses in human pathology, especially by the appearance of strain causing severe acute respiratory syndrome (SARS).

3.4 | Encephalomyocarditis

Experimental encephalomyocarditis was reproduced in 25 monkeys of 4 species.[29] We showed that the virus strain EMC-70 causes changes in monkey brain and myocard. At the acute stage of illness, ECG was similar to cardiogram of infarction patients. Encephalomyocarditis is a serious problem for many primatological organizations. The experimental primate model is actual and used for trials of vaccines and preparations.[30]

3.5 | Hepatitis A

Hepatitis A (HPA) was reproduced in 4 monkey species (rhesus macaques, cynomolgus monkeys, green monkeys, and hamadryas baboons) inoculated with strains isolated from monkeys and 1 strain isolated from a patient.[31] The most significant and studied HPA model is rhesus macaque infected by human HAV. This model is cheaper and more available than its previous analogues in chimpanzees and marmosets. We obtained results on infection chronicity and HAV persistence.[32] Our data brought new knowledge about HPA epidemiology: HAV long-term conservation in immune organisms of sensitive primates allows to consider primates as animal reservoir in intra-epidemic period. Cultural inactivated HPA vaccine offered by German scientists F. Deinhardt and B. Fleming was tested in the rhesus macaque model.[32] Its good protective properties were revealed. In the last years, using vaccines manufactured with similar technology showed their high efficiency in human immunization.

3.6 | Simian hemorrhagic fever

Hemorrhagic fever similar to spontaneous 1 was reproduced by us in macaques with the strain "Sukhumi-64".[33] Problems of infection pathogenesis were studied. We showed the virus tropism to cells of the reticuloendothelial system—monocyte-macrophage system. Death of these cells leads to release of tissue procoagulant and blood coagulation increase. The first stage of hypercoagulation is followed by hypocoagulation. The coagulation profiles are similar to profiles at disseminated intravascular coagulation syndrome.[34] Analogous data were obtained by a number of authors during Ebola hemorrhagic fever research: virus tropism to endothelial cells and to macrophages, and coagulation damage is a result of virus tropism to cells of the monocyte-macrophage system.[35] Comparison of our results with literature data showed that general pathophysiological mechanisms underlie the pathogenesis of various hemorrhagic fevers. Only primates can be considered as an adequate model because in primates disease proceeds in a similar to human way. The strain "Sukhumi-64" is not pathogenic for human, so experimental SHF reproduced with this virus in macaques is proposed by us as the model of human hemorrhagic fevers.[13,34]

4 | CONCLUSION

Today, an interest to the virus and to the model has been increased that is explained by growing epidemic potential of the most dangerous hemorrhagic human fevers and the possibility of their introduction to non-endemic territories.[36] Hemorrhagic fever viruses were added to the list of bioterrorism agents. The situation with Ebola virus causes much trouble. From 1976, when this infection firstly appeared in Sudan, Zaire and other African countries, outbreaks occur every 2-4 years, and lethality is 25%-90%. The largest outbreak, announced by WHO to be Public Health Emergency, took place in West Africa in 2014. Human illness fit with multiple lethal cases of gorillas and chimpanzees in nearest forests. There is the danger of sharp decreasing anthropoid apes in nature.[37] It is established that ill and dead monkeys are the infection source for humans.

Therapeutic and preventive treatments of human hemorrhagic fevers are absent. For testing the developed preparations, the experimental model is necessary. Monkeys are the only animals in which these diseases proceed in a similar to human way, but the direct work with infection agents is very dangerous. There were human lethal cases after laboratory infection.[38] In literature, our model of experimental hemorrhagic fever is discussed as the unique safe and adequate model for the assessment of new preparations. Research in this field is acknowledged to be very important.[39]

Our data show that studies conducted in monkeys of the Sukhum colony are the significant part of great contribution in research of human viral infections and their prophylaxis made by primates.

ORCID

Boris A. Lapin http://orcid.org/0000-0002-5677-3251

REFERENCES

1. Ryazantseva NE. Measles outbreak among monkeys. *Zh Mikrobiol Epidemiol Immunobiol*. 1956;4:88.
2. Lapin BA, Krylova RI. Viral infections in monkeys of Sukhumi colony. In: Ippen R, Schröder H-D, eds. *Verhandlungsbericht des XXII. International Symposium über die Erkrankkunden der Zootiere*. Berlin, Germany: Acad-Verl; 1981:65-68.
3. Lapin BA, Jakovleva LA. *Vergleichende Pathologie der Affen*. Jena, Germany: Fischer; 1964.
4. Lapin BA, Pekerman SM, Iakovleva LA, et al. Hemorrhagic fever in monkeys. *Vopr Virusol*. 1967;12:168-173.
5. Lapin BA, Shevtsova ZV. Research of viral simian hemorrhagic fever. In: Krupovnickas VA, ed. *Materials of IX International Congress on Microbiology*. Vilnus, USSR: Vaizdas; 1966:465-466.
6. Shevtsova ZV. Research of simian hemorrhagic fever etiology. *Vopr Virusol*. 1967;12:47-51.
7. Shevtsova ZV. A further study of simian hemorrhagic fever virus. *Vopr Virusol*. 1969;5:604-607.
8. Palmer AE, Allen AM, Tauraso NM, Shelokov A. Simian hemorrhagic fever. I. Clinical and epizootologic aspects of an outbreak among quarantined monkeys. *Am J Trop Med Hyg*. 1968;17:404-412.
9. Tauraso NM, Shelokov A, Palmer AE, Allen AM. Simian hemorrhagic fever. III. Isolation of viral agent. *Am J Trop Med Hyg*. 1968;17:422-431.
10. Madden DL, Fuccillo DA, Dorosz JA, London WT, Palmer AE, Castellano GA. Antigenic relationship of two strains of SHFV. *Lab Anim Sci*. 1978;28:422-427.
11. Lapin BA, Shevtsova ZV. On the identity of two simian hemorrhagic fever virus strains (Sukhumi and NIH). *Z Versuchstierkd*. 1971;13:21-24.
12. Lauck M, Alkhovsky SV, Bào Y, et al. Historical outbreaks of simian hemorrhagic fever in captive macaques were caused by distinct arteriviruses. *J Virol*. 2015;89:8082-8087.
13. Lapin BA, Shevtsova ZV. To the 50th anniversary of the discovery of the simian hemorrhagic fever and SHF virus. *Vopr Virusol*. 2015;60:5-11.
14. Kuhn JH, Lauck M, Bailey AL, et al. Reorganization and expansion of the nidoviral family Arteriviridae. *Arch Virol*. 2016;161:755-768.
15. Dzhikidze EK, Shevtsova ZV, Krylova RI, Balaeva EY, Voskanian NA, Uvarova VI. Zur Äthiologie der Encephalomyocarditis von Rhesusaffen. *Z Versuchstierkd*. 1974;16:142-149.
16. Shevtsova ZV, Dzhikidze EK, Voroshilova MK, Uvarova VI, Ivanov MT. Characteristics of encephalomyocarditis virus isolated from sick monkeys. *Vopr Virusol*. 1976;5:531-536.
17. Krylova RI, Dzhikidze EK. Encephalomyocarditis in monkeys. *Bull Exp Biol Med*. 2005;139:350-359.
18. Gaskin JM, Jorge MA, Simpson CF, et al. The tragedy of encephalomyocarditis virus infection in zoological parks of Florida. *Proc Annu Am Assoc Zoo Vet*. 1980;1-7.
19. Vasileva VA, Ivanov MT, Rumel NB, Dyachenko AG, Kakubava VV, Danelyan GA. Isolation and biological characterization of an adenovirus of rhesus macaques. *Acta Biol Med Ger*. 1978;37:1281-1287.
20. Vasileva VA, Ivanov MT, Dyachenko AG. Study of herpes virus isolated from rhesus macaques. *Biology (Biologia)*. 1976;10:268.
21. Shevtsova ZV, Korzaia LI, Lapin BA, Krylova RI, Sazhchenko LA. Materials from a disease outbreak among rhesus macaques associated with monkey enterovirus. *Vestn Akad Med Nauk SSSR*. 1986;3:28-30.
22. Goncharuk EI, Shevtsova ZV, Rumel' NB, Krylova RI. Spontaneous coronavirus infection in monkeys. *Zh Mikrobiol Epidemiol Immunobiol*. 1994;Suppl 1:109-114.
23. Shevtsova ZV, Krylova RI, Belova EG, Korzaia LI, Andzhaparidze AG. Spontaneous hepatitis A with a fatal outcome in rhesus monkeys. *Vopr Virusol*. 1987;6:686-690.
24. Lapin BA, Shevtsova ZV, Doroshenko NV. Spontaneous and experimental hepatitis A in Old World monkeys. *J Med Primatol*. 1988;17:177-194.
25. Korzaia LI, Shevtsova ZV, Lapin BA, D'iachenko AG, Krylova RI. Preparation and characteristics of cultured strains of hepatitis A virus from humans and monkeys. *Vopr Virusol*. 1997;42:60-63.
26. Voroshilova MK. Experimental poliomyelitis in monkeys. In: Utkin IA, ed. *Theoretical and Practical Questions of Medicine and Biology in Experiments in Monkeys*. Moscow, Russia: Medgis; 1956:165-178.
27. Sergiev PG, Shroit IG, Chelysheva KM, et al. Materials on measles pathogenesis and vaccinal process. *Acta Virol*. 1966;5:430-439.
28. Goncharuk EI, Shevtsova ZV, Krylova RI, Rumel' NB. Coronavirus infection of monkey as a model of human disease. *Dokl Akad Nauk*. 1992;325:845-848.
29. Dzhikidze EK, Shevtsova ZV, Krylova RI. Experimental encephalomyocarditis in some monkey species. *Exp Pathol*. 1976;12:242-249.
30. Emerson CL, Wagner JL. Antibody responses in two encephalomyocarditis virus vaccines in rhesus macaques. *J Med Primatol*. 1996;25:42-45.
31. Lapin BA, Shevtsova ZV, Krylova RI. Spontaneous and experimental hepatitis A in Old World monkeys and their use for studying this infection. *World Viral Hepat*. 2006;6:3-9.
32. Shevtsova ZV, Flehmig B, Lapin BA, et al. A trial of a hepatitis A cultured inactivated vaccine on rhesus macaques. *Zh Mikrobiol Epidemiol Immunobiol*. 1995;2:55-59.
33. Lapin BA, Shevtsova ZV, Krylova RI. Experimental hemorrhagic fever of monkeys. In: Hofer HO, ed. *Proceedings of the 2nd International Congress of Primatol*. Atlanta, GA: Karger/Basel; 1969:196-203.
34. Lapin BA, Shevtsova ZV. Experimental hemorrhagic fever of macaques as a model of human hemorrhagic fever. In: Lapin BA, Vyshemirskii OI, Klots IN, eds. *Fundamental and Applied Problems of Medical Primatology*. Volume 1. Sochi, Russia: Sterkh; 2016:121-132.
35. Geisbert TW, Young HA, Jahrling PB, Davis KJ, Kagan E, Hensley LE. Mechanisms underlying coagulation abnormalities in Ebola hemorrhagic fever. *J Infect Dis*. 2003;188:1618-1629.
36. Markin VV, Markov VI. Viral hemorrhagic fevers – evolution of epidemical potential. *Zh Mikrobiol Epidemiol Immunobiol*. 2002;1:91-98.
37. Ebola virus devastates Central African ape population. *IPPL News*. 2003;30:13-14.
38. Semina NA, Kovaleva EP. Infection of medical workers with highly infectious disease associated with laboratory introduction. *Epidemiol Vaccine Prophylaxis*. 2005;20:23-28.
39. Johnson RF, Dodd LE, Yellayi S, et al. Simian hemorrhagic fever virus infection of rhesus macaques as a model of hemorrhagic fever: clinical characterization and risk factors for severe disease. *Virology*. 2011;421:129-140.

How to cite this article: Lapin BA, Shevtsova ZV. Monkey viral pathology in the Sukhum colony and modeling human viral infections. *J Med Primatol*. 2018;47:273–277. https://doi.org/10.1111/jmp.12351