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Torovirus infection in animals: a review

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SUMMARY

Massive digestive disorders of neonatal calves, clinically manifested as diarrhea causing severe dehydration, toxemia, immunodeficiency and metabolic disorders, induce huge economic losses in animal husbandry. Etiopathogenetic lesions of the digestive organs are characterized by significant polymorphism, including a wide range of various (physiological, sanitary and infectious) factors. Massive gastroenteritises in neonatal calves are primarily caused by such infectious agents as viruses, bacteria and protozoa. Massive diarrheas are registered in 70–80% of newborn calves by the end of the first day of life. Diseased newborn calves die on day 5–10 and mortality ranges from 15 to 55%. Rotavirus, coronavirus, pestivirus, parvovirus, enterovirus and kobuvirus, along with bacteria, are most frequently detected in faecal samples collected from neonatal calves with diarrhea. Diagnostic and vaccine products for prevention of these infections have been developed in the Russian Federation. At the end of the 20th – the beginning of the 21st century a large number of cattle were imported to Russia from the countries affected with different contagious diseases (USA, Denmark, France, Slovakia, Austria, Hungary, Germany, the Netherlands, Australia, Finland, etc.). Despite the high activity and field effectiveness of vaccines against rotavirus and coronavirus infections and viral diarrhea, massive neonatal calf diarrheas causing significant economic losses were registered in a number of large-scale livestock farms. Torovirus as well as the above-mentioned pathogens were detected in fecal samples from diseased calves. This report provides data on torovirus infection indicating a wide geographical distribution of animal torovirus in many countries of the world. All this suggests the need to take into account torovirus infection when conducting epizootological investigations in farms affected with massive gastrointestinal diseases of neonatal calves.

Keywords: review, torovirus, calves, piglets, horses, dogs, cats, electron microscopy, gastrointestinal pathology, fecal-oral transmission route

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Проблема торовирусной инфекции животных (обзор литературы)

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РЕЗЮМЕ

Большой экономический ущерб животноводству наносят массовые нарушения функции пищеварения новорожденных телят, клинически проявляющиеся диареей, обуславливающей развитие выраженной дегидратации, токсемии, иммунодефицитов и нарушения обмена веществ. Этиопатогенетические поражения органов пищеварения отличаются значительным полиморфизмом, включающим широкий спектр различных факторов, в том числе физиологических, санитарно-гигиенических и инфекционных. Главной причиной массовых гастроэнтеритов новорожденных телят являются такие инфекционные агенты, как вирусы, бактерии и простейшие. Массовые диареи регистрируются у 70–80% новорожденных телят уже к концу первых суток. Гибель больных новорожденных телят наступает на 5–10-е сут и составляет от 15 до 55%. Чаще всего в пробах фекалий, отобранных от больных диареей новорожденных телят, наряду с бактериями выявляют ротавирус, коронавирус, пестивирус, парвовирус, энтеровирус и кобувирус. Для профилактики указанных инфекций в Российской Федерации были разработаны диагностические и вакцинные препараты. В конце XX – начале XXI века на территорию России было завезено большое количество крупного рогатого скота из различных стран мира (США, Дания, Франция, Словакия,

Австрия, Венгрия, Германия, Нидерланды, Австралия, Финляндия и др.), неблагополучных по ряду инфекционных болезней. Несмотря на высокую активность и полевую эффективность вакцин против рота-, коронавирусной инфекций и вирусной диареи, в ряде крупных животноводческих хозяйств были зарегистрированы массовые диареи новорожденных телят, становившиеся причиной значительного экономического ущерба. В пробах фекалий от больных телят кроме перечисленных возбудителей был обнаружен торовирус. В данном сообщении приведены данные о торовирусной инфекции, свидетельствующие о широком географическом распространении торовируса животных во многих странах мира. Все это говорит о необходимости учета торовирусной инфекции при проведении эпизоотологических расследований в неблагополучных по массовым желудочно-кишечным заболеваниям новорожденных телят хозяйствах.

Ключевые слова: обзор, торовирус, телята, поросята, лошади, собаки, кошки, электронная микроскопия, патология желудочно-кишечного тракта, фекально-оральный путь заражения

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Gastrointestinal diseases of neonatal calves are ranked as the leading cause of economic damage and remain a topical issue in animal husbandry. This pathology is generally manifested as diarrhea and has an infectious nature, it is caused by various etiological agents and develops as mixed infections.

Along with bacteria, rotavirus, coronavirus, pestivirus (viral diarrhea virus – diseases of bovine mucosa), parvovirus, enterovirus and kobuvirus are most frequently detected in fecal samples collected from neonatal calves with diarrhea [1–9]. Inactivated vaccines were developed in the Russian Federation to prevent rotavirus and coronavirus infections, as well as viral diarrhea – a mucosal disease caused by genotype 1 virus [1–3, 10]. Currently, cases of the circulation of pestiviruses belonging to more than 15 subgenotypes of all 3 genotypes have been registered in the country [10]. All this indicates significant difficulties in determining the etiology of gastrointestinal pathology in neonatal calves. Such a variety of diarrhea agents significantly complicates the diagnosis, resulting in low effectiveness of prevention and leading to significant economic damage.

Torovirus was first isolated in Berne (Switzerland) in 1972 from a rectal swab of a newborn horse with diarrhea. At first this pathogen was named "Berne virus" by the place where sampling was performed, later it was classified as *Equine torovirus* (EToV) [11, 12]. In 1979, a virus similar in structure was detected in feces from diarrheal calves in Breda (USA), now known as *Bovine torovirus* (BToV). On this farm a severe form of diarrhea had been registered in young cattle for several months [13, 14].

In 1984 a virus with a similar structure was detected in rectal specimens from children with diarrhea [15]. A few years later, in 1997, torovirus was identified by electron microscopy in stool samples from 3-week-old piglets with diarrhea on a pig farm in the UK [16]. Subsequently, this pathogen (*Porcine torovirus*, PToV) was detected in 6–40% of fecal specimens collected from diarrheal piglets in the Netherlands, Canada, USA, South Africa, China, Belgium, Italy, Hungary, Spain and South Korea [17]. Antibodies to the torovirus were found in 50–100% of sera from piglets of different age. Toroviruses were also detected in fecal samples of other animal species with diarrhea [18–21]. It was found that there is a close genetic relationship between the toroviruses of pigs, cattle, horses, dogs and cats. It is believed that interspecies recombination between these pathogens is possible [16, 22, 23]. A number of researchers believe that toroviruses have zoonotic potential [13, 17, 24]. According to the current virus classification, toroviruses belong to the genus *Torovirus*, which is part of the family *Tobaniviridae*[1], although it was previously referred to the family *Coronaviridae* [23, 25, 26].

Toroviruses are polymorphic, enveloped, peplomer-bearing particles with a diameter of 120–140 nm. The shape of a virion is a biconcave disk (Fig.). The genome of toroviruses is represented by an infectious single-stranded positive RNA. The tubular nucleocapsid is bent into an open torus (swelling, node), hence the name of the pathogen is "torovirus" [2, 13, 25, 27, 28].

The buoyant density of virion in sucrose is 1.14–1.18 g/mL. Toroviruses are resistant to phospholipase C, trypsin, chymotrypsin. Triton X-100 and organic solvents destroy toroviruses. They persist for a long time at from minus 20 to minus 70 °C and pH of 2.5 to 10.5. Repeated cycles of freezing and thawing result in loss of peplomers and desintegration of virions [25].

Epidemiological properties of torovirus infection include long-term shedding of the pathogen from diseased animals and virus-carriers. Cattle, pigs and horses are the natural hosts of toroviruses. The main sources of the pathogen are diarrheal calves under 30 days of age [29, 30]. The virus sheds in feces and nasal discharge of diseased

[1] International Committee on Taxonomy of Viruses (ICTV). Available at: https://ictv.global/taxonomy.

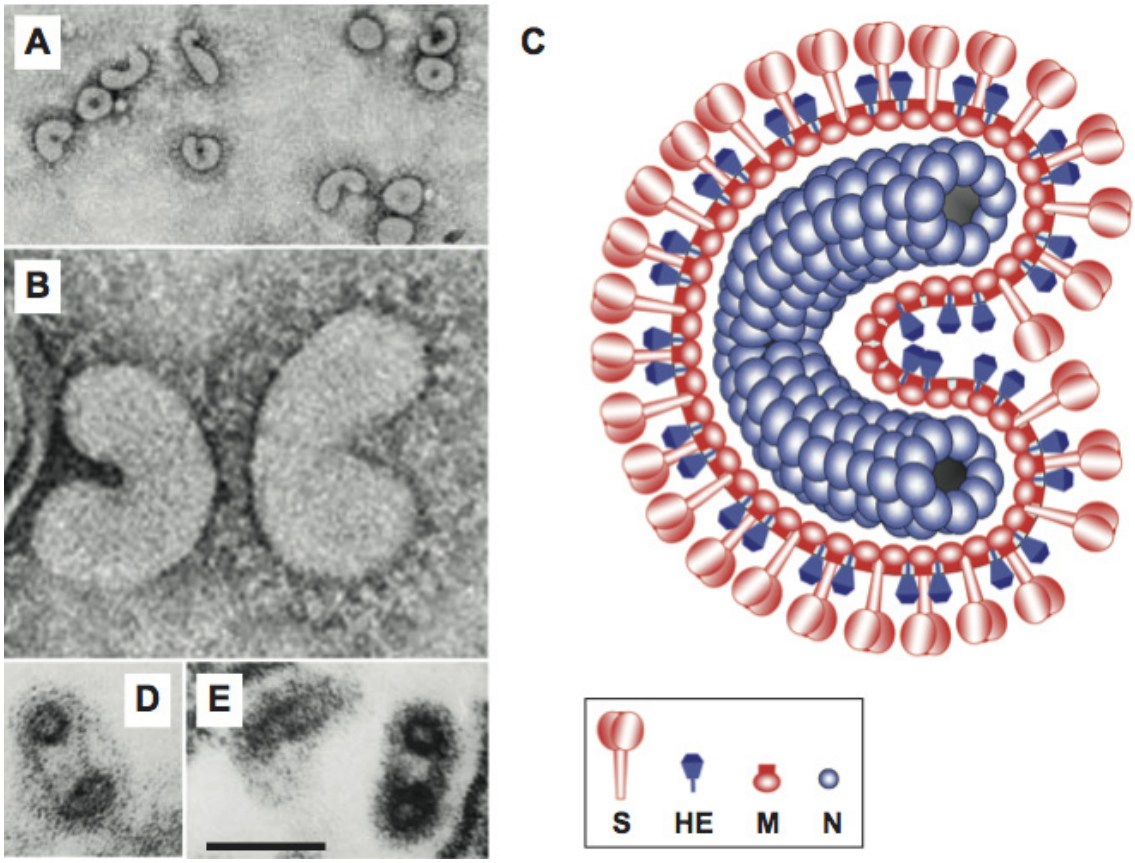

Fig. Electron micrograph of the virion and structure of the torovirus:
S-protein – glycoprotein spike;
HE-protein – hemagglutinin-esterase protein complex involved in virus-cell fusion and suppression of immune response;
M-protein – membrane protein;
N-protein – nucleoprotein (https://ictv.global/sites/default/files/inline-images/f68-08-9780123846846.png)

animals [14]. Feed and water contaminated with torovirus can be considered transmission factors. Calves are mainly infected via fecal and oral route [9, 31, 32].

Entering the gastrointestinal tract, toroviruses attach to enterocytes of the apical surface of the villi of the distal jejunum and ileum, as well as the large intestine [12, 33]. The virus enters enterocytes through receptor-mediated endocytosis. Replication occurs in the cytoplasm of enterocytes. The replication cycle of toroviruses takes around 10–12 hours to complete. Toroviruses are released from enterocytes into the intestinal lumen through pinocytosis. The characteristic torus morphology of BToV is only observed in extracellular viral particles or in vacuoles near the cell surface. Necrosis of the crypt epithelium, desquamation of villous enterocytes and their atrophy are recorded during torovirus infection. Intestinal lesions caused by the infection result in hypersecretory and malabsorptive diarrhea [27, 33, 34].

Torovirus is found in the feces of diseased calves, and in some cases also in fecal samples taken from clinically healthy young animals from farms affected with gastrointestinal diseases. It can be assumed that the test samples were collected from calves at different stages of the pathological process [35]. Torovirus was detected in fecal preparation after three weeks [13, 36]. Natural infection usually occurs in 2–5-day-old calves, but calves up to 4 months of age are apparently susceptible to infection as well [37–39].

This virus was detected in fecal specimens not only from newborn calves with diarrhea, but also from clinically healthy adult cattle [40–42]. The clinical signs observed during natural infection are identical to those demonstrated during rotavirus and coronavirus infections [3–6, 43]. Noroviruses, neboviruses and kobuviruses, along with toroviruses, were detected in feces of newborn calves with diarrhea [29, 31]. Toroviruses were detected in fecal specimens and nasal swabs of fattening cattle [8, 14, 31, 37].

The Japanese researchers first isolated the torovirus in a human rectal adenocarcinoma cell line (HRT-18) from the ileum contents of a calf with diarrhea. The cytopathic effect appeared on day 2–3 after virus inoculation. The torovirus accumulated in the titers of 5.8–6.8 lg $TCID_{50}$/mL after passage 3 in cell culture. Electron microscopy showed that toroviruses appear as oval particles ranging from 100 to 170 nm in diameter. Oval and elongated particles of approximately 100 to 170 nm in diameter with kidney-shaped projections were detected in the supernatant of the infected culture,

and torovirus-like (tubular and thorusnucleocapsid) structures were detected in infected cells using electron microscopy. An antiserum against bovine torovirus (BToV) reacted with the infected cells and neutralized the isolate of this pathogen [44].

Epidemiological investigations conducted in farms affected with mass diarrhea of newborn calves include testing of blood sera from diseased animals for the presence of virus antibodies using enzyme-linked immunosorbent assay (ELISA). To study the prevalence of torovirus infection in the Netherlands and the FRG, serological tests of blood serum samples (n = 1,313 and n = 716, respectively) collected from breeding and fattening herds were conducted. At the same time, antibodies were detected in 94% of adult cattle, 90% of newborn calves had high levels of maternal antibodies, which waned until the age of 3 months [45].

In order to determine the role of bovine torovirus in the development of diarrhea, the Japanese researchers studied the prevalence of this pathogen. Fecal samples of healthy and diarrheal calves were collected for testing using reverse transcription polymerase chain reaction. Torovirus was detected in 17.5% of samples from diseased animals and in 7.0% of samples from healthy calves. These data showed that BToV circulates in Japan mainly among calves under 2 weeks of age [35, 46]. This pathogen was also detected in fecal samples from newborn calves with diarrhea in Canada [29]. In 2009–2014 fecal specimens from 235 newborn calves were tested in Turkey. The torovirus RNA was detected in 4.7% of samples [32]. Subsequently, BToV was found in 16.7% of fecal samples collected from 72 calves from various farms in Turkey. In the phylogenetic tree, the virus isolates recovered from faecal samples of calves in Europe, America, Southeast Asia and Turkey were found to be divided into separate branches [47].

Neonatal calf diarrhea causes significant economic damage to livestock breeding in South Korea [38, 41]. Diarrhea was registered in one of the farms where 207 young cattle were kept. Genomes of pathogens of various infectious diseases were identified in fecal samples of 164 (79.2%) animals. Rotavirus, coronavirus, torovirus, parvovirus, norovirus, kobuvirus, pestivirus were detected in 69.9% of samples, *Escherichia coli* and *Clostridium* bacteria were detected in 31.8% of samples, protozoa (eimeria) in 31.7% of samples, fungi in 14.0% of cases [38]. These test results indicate a mixed etiology of this pathology.

Toroviruses were also detected in the tests for determining the etiology of diarrhea in newborn calves on Chinese farms [39]. BToV was isolated from faecal samples of calves with diarrhea in Croatia [28], Austria [22], from newborn calves and piglets in Hungary [36]. As numerous studies show, animal torovirus infection was diagnosed worldwide: in Switzerland, USA, India, Iran, Canada, Germany, France, Belgium, Great Britain, Costa Rica, the Netherlands, New Zealand, South Korea, Turkey, Japan, Brazil, Finland, Egypt, South Korea and the countries of South Africa. In infected farms, torovirus-induced diarrhea is registered in 50–60% of neonatal calves, resulting in death of 5–10% diseased calves. In most cases, the disease lasts for 5–10 days [14, 29, 32, 33, 35, 37, 38, 41, 42, 44–46, 48–51]. The obtained study results indicate a wide distribution of torovirus in livestock farms.

Tests of fecal samples collected from newborn calves with signs of diarrhea in several large livestock farms in the Russian Federation, conducted using electron microscopy, revealed, besides rotavirus and coronavirus, viral particles morphologically similar to astroviruses [43] and toroviruses [6].

Laboratory diagnosis of torovirus infection is based on test results of fecal samples by polymerase chain reaction and detection of the pathogen in epithelial cells of the small intestine by electron and immunoelectron microscopy. BToV was found to replicate in MDBK cells (calf kidney cell culture), HRT-18 (human rectum adenocarcinoma cell culture cell culture) and calf thyroid gland. Currently, there are no specific preventive tools for torovirus infection. Timely feeding with colostrum containing colostral antibodies induces protection of newborn calves from this infection. Along with this, compliance with sanitary and hygienic requirements and biosafety measures, as well as isolation of diseased animals are recommended. Toroviruses are believed by some researchers to play a certain role in the pathogenesis of diarrhea of mixed etiology in adult cattle [40–42, 45].

CONCLUSION

The presented data indicate a wide geographical distribution of torovirus in cattle, pigs, horses and other livestock species in different countries worldwide. Torovirus infection is manifested by diarrhea of neonatal animals, which leads to mass mortality of livestock and causes great economic damage to livestock farms. Torovirus sheds in faeces and nasopharyngeal secretions of diseased animals. The main route of infection of newborns is fecal-oral. Lesions of the intestinal mucosa in neonatal animals caused by torovirus infection result in the development of hypersecretory and malabsorption diarrhea. Clinical signs and pathologic-anatomical changes due to torovirus infection do not differ from those observed in rotavirus, coronavirus infections of newborn calves and viral diarrhea – diseases of bovine mucosa that are widely distributed in the Russian Federation. Toroviruses play a specific role in the pathogenesis of diarrhea in adult cattle. Data on the close genetic relationship of toroviruses of cattle, pigs, horses, cats and dogs suggest a high probability of cross-infection in these animals, which shall be taken into account when clarifying the etiology of mass diarrhea of these animal species. The torovirus infection is epizootologically characterised by long-term shedding of the pathogen in feces and nasal discharge of diseased animals and virus carriers in high concentrations. Factors of torovirus transmission may include feed, water and animal handling items contaminated with the pathogen. All this indicates the need to take into account torovirus infection when conducting epidemiological investigations in farms affected with mass gastrointestinal diseases of newborn calves, piglets, foals, as well as diseases of cats and dogs with diarrheal syndrome, based on the data of some researchers that toroviruses have zoonotic potential.

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