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ATYPICAL PORCINE PESTIVIRUS (*Pestivirus K*) — A NEW CHALLENGE FOR PIG FARMING

(review)

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Abstract

Pestiviruses are highly variable RNA viruses of the genus *Pestivirus*, family *Flaviviridae*. The genus *Pestivirus* includes 11 species, from *Pestivirus A* to *Pestivirus K* (B.G. Orlyankin et al., 2020; D.B. Smith et al., 2017; A.M.Q. King et al., 2018). In the infectious pathologies of pigs, pestiviruses are highly important due to significant economic losses. Over the past two decades, many previously undescribed pestiviruses have been found in domestic pigs and wild boars. Due to the tendency to rapid spread, they can cause a serious threat to pig production. In 2015, in the framework of the Porcine Reproductive and Respiratory Syndrome Virus genetic diversity project in the US, an atypical porcine pestivirus (*Pestivirus K*) was first identified in blood serum by metagenomic sequencing. Initially, it was assumed that pigs infected with atypical pestivirus did not show clinical signs of the disease. However, the experiments on the study of atypical pestivirus infectious properties showed that the pestivirus causes congenital tremor (CT) type A-II in piglets (B.L. Arruda et al., 2016; A. de Groof et al., 2016; A. Postel et al., 2017). Adult domestic pigs and wild boars are also susceptible to the virus. Atypical porcine pestivirus is transmitted vertically and horizontally and is widespread in many countries of Europe, America and Asia. In Russia, atypical porcine pestivirus has not been diagnosed in pigs. The phylogenetic analysis of the genome of all known isolates revealed 3 genetic groups (1^{st}-3^{d}) and seven subgenotypes within the 1^{st} genetic group (1.1-1.7) of the virus (F. Yuan et al., 2021). The first genetic group includes all isolates identified in the USA, Europe and several isolates from China. The second and third genetic groups are isolates from China only. The circulation of atypical porcine pestivirus in herds can complicate the differential diagnosis of classical swine fever, due to some similarity of symptoms, the congenital tremor particularly. Consequently, the knowledge of the epidemiology of the atypical porcine pestivirus in different geographic regions will help optimization of its control and prevention of spreading. The review covers current data of the etiology, distribution, clinical manifestations, diagnosis and prevention of the atypical porcine pestivirus infection.

Keywords: atypical porcine pestivirus, identification, differential diagnosis, congenital tremor, pigs, classical swine fever, diseases prevention

Pestiviruses (genus *Pestivirus*, family *Flaviviridae*) belong to RNA viruses with a single positive strand of RNA (+ssRNA). Previously, only three representatives of this genus were known, including bovine viral diarrhea virus (BVDV), border disease virus (BDV) and classical swine fever virus (CSF). swine fever virus, CSFV) [1]. It was assumed that pestivirus infection in pigs is caused only by the classical swine fever virus, a transboundary, highly contagious and economically significant disease for industrial pig production in many countries [2, 3]. However, given the close relationship of pestiviruses and their ability for interspecific

transmission, infection of pigs by other representatives of this genus could not be ruled out. Thus, back in 1964, the bovine viral diarrhea virus was identified in pigs in Australia [4, 5]. Infection of pigs with VDV under natural conditions has also been described in the USA [6], the Netherlands [7], China [8] and Brazil [9]. During routine serological monitoring of CSF in Spain [10] and Japan [11], sheep border disease virus was detected in pigs. Infection with a HoBi-like pestivirus has been experimentally reproduced [12, 13]. Infection of pigs with ruminant pestiviruses does not cause obvious clinical signs, but the circulation of such pestiviruses among livestock makes the differential diagnosis of classical swine fever difficult [9]. In recent years, outbreaks of emerging viral infections in pigs have become more frequent, posing a serious threat to pig production. Thus, in 2003, a severe outbreak of a disease of unknown etiology occurred in Australia, which was characterized by stillbirths, pre-weaning mortality and the birth of mummified and weak fetuses with porcine myocarditis syndrome. The causative agent of the disease was identified only in 2007 and was named Bungowannah virus [14, 15]. Another pestivirus, *Linda virus* (lateral-shaking inducing neuro-degenerative agent, a neurodegenerative agent that causes lateral tremor), was discovered in southeastern Austria in Styria in piglets with congenital tremor [16, 17]. Congenital tremor (CT) (Myoclonia Congenita) is a neurological disease of newborn piglets, which manifests itself in the form of tremor of the skeletal muscles of the head and trunk. It manifests itself both locally and generally [18-21]. The first report of congenital tremor in piglets dates back to 1922 [18]. Those born with this trait were known as dancing piglets or shaker piglets [18, 22]. Based on the nature of pathological damage to the central nervous system, two types of congenital tremor, A and B are distinguished. With CT type A, histopathological changes in the brain and spinal cord are observed, with CT type B no such changes occurred [18-22]. CT type A, in turn, is divided into five subtypes (I-V). Subtype A-I is caused by the CSF virus [18], subtype A-III is considered a genetic defect in male Landrace pigs, CT A-IV is also a hereditary type of pathology, which is manifested by hypomyelination brain and spinal cord of British Saddleback pigs [18, 19, 22]. The cause of CT subtype A-V is poisoning of pregnant sows with trichlorfon, which was previously used to treat pigs from ectoparasites [18]. For many years, the cause of CT A-II remained unknown. It was believed that the pathology could be caused by a virus [20]. In 2015, during experimental infection of pigs, it was found that type A-II CT develops during transplacental infection of sows with a new atypical porcine pestivirus (APV) [23, 24].

This review summarizes current information on the distribution of atypical porcine pestivirus (*Pestivirus K*), characteristics of the pathogen, clinical manifestations, diagnosis and prevention of infection.

Etiology and modern classification of pestiviruses. In 2015 in the USA, as part of a project to study the genetic diversity of the porcine reproductive and respiratory syndrome (PRRS) virus, B.M. Hause et al. [23] examined 182 porcine serum samples using metagenomic sequencing. In analyzing their results, the authors determined that the nucleotide sequences found in five sera obtained in 2014 from Nebraska, Arizona, North Carolina, Minnesota, and Kansas had 68% similarity to the genome sequences of the bat pestivirus *Rhinolophus affinis* (*RaPV*) [25] and 25-28% similarity with the VD, PB and CSF viruses. The authors found that the virus they identified belongs to the genus Pestivirus and is widespread in the United States [23]. Attempts to isolate it in cell cultures at that time were unsuccessful. The pathogenicity of the new virus remained unknown. In 2016, B.L. Arruda et al. [24] reproduced APS infection and showed that infection of individuals during pregnancy leads to the birth of piglets with congenital tremor type A-II. Since then, APS has been associated with

A-II CT.

In 2018, the taxonomy of the genus *Pestivirus* was revised and ratified by the International Committee on Taxonomy of Viruses (ICTV) [27, 28]. An atypical pestivirus of pigs was isolated into a separate nosological unit and named *Pestivirus K*. Other representatives of the genus *Pestivirus* of the *Flaviviridae* family are *Pestivirus A* (viral diarrhea virus type 1), *Pestivirus B* (viral diarrhea virus type 2), *Pestivirus C* (classical diarrhea virus swine fever), *Pestivirus D* (sheep border disease virus), *Pestivirus E* (pronghorn pestivirus), *Pestivirus F* (Bangowanna virus), *Pestivirus G* (giraffe pestivirus), *Pestivirus H* (viral diarrhea virus type 3, HoBi-like pestivirus), *Pestivirus I* (Aydin-like pestivirus) and *Pestivirus J* (rat pestivirus) [26-30].

Due to the discovery of new pestiviruses in both pigs and other animals, A. Postel et al. [30], having studied the genetic relationship of pestiviruses, propose expanding the number of their species by including in the taxonomy *Linda virus* (*Pestivirus L*), Phocoena pestivirus (*Pestivirus M*), sheep pestivirus isolated in Tunisia (*Pestivirus N*), sheep pestiviruses isolated in Italy (*Pestivirus O*), pangolin pestivirus (*Pestivirus P*), rodent pestiviruses (*Pestivirus Q*, *Pestivirus R*) and bat pestiviruses (*Pestivirus S*) [30].

Distribution of atypical porcine pestivirus. APS was first discovered in 2015 in the United States [23]. Since then, its circulation in domestic pig herds has been reported in the Netherlands [31], various states in the USA [32-34], Austria [35], China [36-40], Spain [41], South Korea [42], Brazil [43-45], Great Britain [46, 47], Taiwan [47], Canada [48, 49], Hungary [50], Japan [51], Italy [52], Serbia [47], Sweden [53], Switzerland [54], Denmark [55], and Germany [47, 56-58]. In Sweden, South Korea, Italy, Spain and Germany, atypical porcine pestivirus was also found in wild boars [52, 59-62]. In Russia, infection caused by atypical porcine pestivirus has not been described.

In Germany, in 2016, APS was first identified in naturally infected piglets born with CT A-II and in clinically healthy adult pigs. The APS genome was found in blood sera, in various parenchymal organs, as well as in the cerebellum and peripheral nerves of newborn piglets with CT [56].

In the Netherlands, on one of the farms in 2012, A. de Groof et al. [31] observed severe flare of CT types A-I–A-V. The mortality rate of piglets was 60%. Long before the outbreak (in November 2009 and December 2010), several piglets on the same farm were diagnosed with CT A-II. Single outbreaks of CT were noted until 2016. The nucleotide sequences of the viral genome, which were found in the blood sera of piglets born with CT, were studied in 2012 using the VIDISCA-454 method (Virus discovery cDNA-AFLP) and showed little similarity with the genome of pestiviruses. After the nucleotide sequences of the genome of the American strain of the APS virus became available in GenBank (https://www.ncbi.nlm.nih.gov/genbank/), it became clear that the cause of CT outbreaks on the farm was APS. In addition, to determine the relationship between CT and APS, the authors of the cited study conducted an experimental infection of pigs. This led them to conclude that transplacental infection of sows results in the birth of infected piglets with CT symptoms that shed the virus in their feces [31].

In China, APS was first discovered in 2017 on a pig farm in Guangdong province during a CT study of blood serum and organs of piglets. J. Yuan et al. [37] reported that APS mainly accumulates in the submandibular lymph nodes of newborn animals. Currently, APS infection is considered widespread in China and is found in almost all provinces [63-66].

In 2017, Austria reported circulating APS in piglets with CT. The research was carried out in 2015-2016. Infection with the virus resulted in a 10% increase

in piglet mortality. ELISA (enzyme-linked immunosorbent assay) revealed antibodies against APS in both piglets and adult pigs. Quantitative reverse transcription PCR (RT-qPCR) analysis showed that large amounts of viral RNA were present in the saliva and semen of adult pigs. In addition, in a study of archival samples obtained in 2013 from pig farms in Lower and Upper Austria from animals with similar symptoms, APS was identified, indicating the circulation of this virus since 2013 [35].

In Spain, the virus was detected in a 2-day-old pig with CT symptoms in 2017, as well as in a retrospective analysis of pig blood sera obtained back in 1997 [41].

In 2018, scientists from Canada also reported the discovery of APS in an outbreak of the disease with symptoms of congenital tremor of subtype A-II in 2-day-old Yorkshire-Landrace piglets. A-II CT in piglets had not previously been reported in Canada. Infected piglets showed severe clinical signs but no stillbirths were observed. Mortality of piglets in litters with CT symptoms reached an average of 24.6% (15 of 61), ranging from 13.3% (2 of 15) to 41.2% (7 of 17), compared with an average mortality of 12 piglets, 7% for litters from other sows on the farm [48].

L. Denes et al. [50] suggest that APS has been circulating in Hungary since 2005. The authors examined collected formalin-fixed organs from piglets with CT symptoms and determined the etiology of disease outbreaks on different farms in Hungary in 2005, 2007, 2010 and 2016-2018. According to an epidemiological study, the seroprevalence of pigs for APS was 37% in Germany, 17.5% in Italy, 7.0% in Switzerland, and 2.3% in the UK. The prevalence of APS among wild boars in Germany, Spain and Italy varies from 0.23% to 52% [57, 59, 67].

Genetic and antigenic characteristics of atypical porcine pestivirus. The genome of the atypical porcine pestivirus is represented by a single-stranded RNA molecule of positive polarity (length 11-12 kb), has one reading frame flanked by 5′- and 3′-untranslated regions (UTR). The open reading frame encodes four structural (C-Erns-E1-E2) and eight nonstructural (Npro-p7-NS2, NS3-NS4A-NS4B-NS5A-NS5B) proteins [21, 22, 25, 26, 29]. The genome organization of APC and all members of the *Pestivirus* genus is similar (with the exception of the pestivirus *Phocoena* found in the guinea pig, which lacks the gene encoding the Npro protein in its genome) [68].

In all pestiviruses, the 5′-UTR begins with a sequence that is capable of forming a stable stem-loop structure [26, 69]. With a thorough genetic analysis of the detected atypical porcine pestivirus using NGS technology, B.M. Hause et al. [23] determined that the 5′-UTR of APS contains only 125 nt and significantly shorter than those of other pestiviruses (370-498 nt). Using the rapid amplification of cDNA ends (RACE) method for APS-positive samples, the authors were still unable to determine the reason for the short size of this region. The length of the 3′-UTR was 245 nt. and corresponded to those of other pestiviruses (200-500 nt) [23].

A feature of the genus *Pestivirus* that distinguishes it from other genera of the *Flaviviridae* family is the presence of the Npro protein, which suppresses the production of antiviral interferon IFN-α/β, disrupting the functioning of the interferon regulatory factor IRF3 and IRF7 signaling [26, 69, 70]. The Npro protein of CSFV and VD viruses is known to be involved in the suppression of IFN-β responses [70, 72]. C. Mou et al. [73] examined the effect of APS Npro protein on the regulation of IFN-β production and found that APS Npro reduced IFN-β production mainly by blocking IRF3 activation. The N-terminal amino acids 31-51 of Npro APS are associated with suppression of the IFN-β response [73]. The nonstructural protein Npro is the very first synthesized protein, which is released

from the formed polypeptide chain during its autoproteolytic cleavage between amino acid residues Cys168 and Ser169. According to B.M. Hause et al. [23] who used the pairwise protein alignment method, a conserved triad of amino acid residues characteristic of Npro pestiviruses (Glu22, His49, Cys69) was identified in APS at positions Glu20, His69, and Cys89 [23, 71]. Despite the conservation of sites of catalytic activity and cleavage sites, the Npro protein of APS did not have significant similarity to the Npro of other pestiviruses (only 9-18% pairwise amino acid identity) [23].

Nucleocapsid protein C has RNA chaperone activity and packages RNA into virions. In APS, compared to other pestiviruses, protein C is longer (111 aa vs. 97-102 aa). The isoelectric point of protein C of APS is similar to that of other pestiviruses (pI in the range of 10.0-10.4) [23, 71].

The Erns protein is another unique protein found only in pestiviruses. In contrast to Npro, Erns is second only to NS3 in terms of conservation among all pestiviral proteins, indicating its important role in the pestivirus life cycle and resistance to modification [70-74]. It is known that Erns has ribonuclease activity against single-stranded and double-stranded RNA, while in the structure of the domain that determines the catalytic activity, Erns is similar to T2 ribonucleases of plants and fungi [75]. T2-RNases are mainly monomeric glycosylated proteins (20-40 kDa) without strict substrate specificity, maximally active in an acidic environment (pH 3.5-6.5). Several biological functions of T2 RNases (both dependent and independent of catalytic activity) have been identified, including cleavage of self-RNA and modulation of the host immune system [75]. The active domain contains the amino acid residues His321, His364, Glu365, Lys368, and His369 [71]. The ectodomain contains nine conserved cysteine residues forming four conserved intrachain disulfide bridges. Using the example of the NADL strain of the VD virus lacking Cys171, it was shown that the interchain disulfide bridge is not essential for the viability of the virus. In the APS genome the T2-RNase domain was identified in the Erns region from aa 319 to 373; the similarity to the Erns proteins of other pestiviruses was 32.9-39.0% [23].

E1 is a structural protein the independent function of which is unknown [26, 69]. Most often, the properties of E1 were analyzed through its interaction with two other envelope proteins, E2 and Erns. E1 is a 25-33 kDa protein (depending on the pestivirus species) with a transmembrane anchor [26]. Together with the E2 protein, it forms heterodimers with a disulfide bond, which play an important role in the penetration of pestivirus into the cell. Heterodimer formation is proposed to occur through interactions between the C-terminal transmembrane domains of the E1 and E2 proteins [26, 69, 71].

Structural glycoprotein E2 is an immunodominant protein of pestiviruses and is important for the formation of protective immunity [26, 71, 78]. The E2 glycoprotein APS plays a major role in this, since it causes the formation of the largest amount of virus-neutralizing antibodies during natural infection of pigs and, possibly, during vaccination [71, 78, 79]. When developing a subunit vaccine based on the APS E2 protein and testing it on laboratory mice, H. Zhang et al. [79] showed that immunized mice mount cellular (Th2-dominant) and humoral immune responses to APS, but further studies are needed to determine the effectiveness of this vaccine in protecting pigs against infection. According to B.M. Hause et al. [23], E2 of APS is 54% identical to E2 of pestivirus RaPV. The size of E2 APS is 241 and 244 aa, which is smaller than that of other pestiviruses (373-378 aa). A deletion in the region encoding the N terminus of APS and pestivirus RaPV E2 results in the loss of the immunoglobulin domains previously described in VVD [80, 81]. Penetration of pestiviruses into cells occurs through receptor-mediated endocytosis. It is known that the VD virus attaches to cells through the

interaction of the E2 glycoprotein with the membrane protein CD46, which acts as an APS receptor [82]. Previously, C. Drager et al. [83] suggested that the penetration of CSFV into cells also occurs with the participation of the cellular receptor CD46 and the glycosaminoglycan heparan sulfate, which acts as an additional receptor. However, G.N. Cagatay et al. [84] refuted this assumption. In their opinion, the CSF and Bangovanna viruses use a different method of entry into the cell, and CD46 does not function as a cellular receptor common to porcine pestiviruses [84] and serves as the main cellular receptor only for APS.

The p7 protein is a small hydrophobic peptide 61-62 aa long, which functions as a viroporin necessary for APS replication in vitro and virulence in vivo. The amino acid similarity of the p7 protein in APS and the pestivirus RaPV is 67% [23].

NS2 is a cysteine autoprotease responsible for proteolysis at the interface of the NS2 and NS3 proteins. NS2 APS has significant amino acid similarity (60%) only with NS2 RaPV; for other pestiviruses this value is only 10-15% [23, 71]. In VD virus, the protease activity of NS2 is due to the presence of the catalytic triad His1447, Glu1462, and Cys1512 (26). Two members of this triad, His1447 and Glu1462, can be identified in NS2 APS (His1237 and Glu1253) [71]. In NS2 APS there is no cysteine residue, but can be compensated by a cysteine residue at position 1280, which shortens the amino acid segment between the Glu and Cys 23 residues [23, 71]. The autoprotease function of NS2 depends on the cellular cofactor Jiv, which is required for the replication of noncytopathogenic pestiviruses [26, 69, 71]. However, this function for NS2 APS has not yet been studied.

NS3 is a chymotrypsin-like serine protease that catalyzes cleavage in both cis and trans. The NS3 protein is identical in APS and RaPV (74%). The similarity of NS4a in APS and RaPV is 61%, in APS and other pestiviruses it is 29-33%. The amino acid identity of NS4b and NS5b of APS and other pestiviruses is 36-45%, whereas NS5a is less conserved (12-17% similarity with other pestiviruses) [23].

In epidemiological studies and in the development of means for the prevention and control of pathology caused by atypical swine pestivirus, it is important to classify the antigenic and genetic groups of isolates from different geographical areas. Phylogenetic analysis of partial and complete genome sequences provides more detailed information about isolates than serological methods and allows detailed discrimination between virus genotypes and subgenotypes. To date, based on the analysis of 76 complete genomes and 16 partial genome sections of APS isolates discovered from 2015 to 2021, three main genetic groups (genotype 1-3) and 7 subgenotypes within genotype 1 (subgenotype 1.1-1.7.) have been identified [67]. Phylogenetic analysis by F. Yuan and L. Wang [67] shows that different genotypes and subgenotypes of APS circulate in the same country. The first genetic group includes all isolates found in the USA, Europe and several isolates from China. The second and third genetic groups are represented only by isolates from China [67].

Clinical signs and modes of transmission of atypical porcine pestivirus. Horizontal and vertical transmission routes of APS have been described [22, 24, 60, 84]. Research by B.L. Arruda et al. [24] and A. de Groof et al. [31] showed that the vertical pathway is responsible for the occurrence of congenital tremor in newborn piglets. Some piglets born with tremors resolve symptoms by 3-14 weeks, but as noted, these piglets shed the virus through feces and saliva [24, 31, 35, 60]. When sick piglets are kept with healthy ones, the latter become infected. It is assumed that the virus can also be transmitted through care items, but this issue has not been sufficiently studied [24, 35, 56] and further research into the routes of transmission of the infectious agent is necessary.

The main clinical sign of naturally infected piglets is congenital tremor. In adult pigs, infection is usually subclinical [23, 24, 56]. Data on postnatal and transplacental infection are insufficient. Experimental infection of pregnant sows was carried out on the 32nd, 45th and 62nd days of gestation [24, 31]. In sows, the infection occurred without clinical signs, but viremia was detected [24, 31, 56], piglets were born with congenital tremors [22, 24, 31, 56], and in some cases abortions and stillbirths occurred [22, 31].

In newborn piglets, clinical signs manifest differently. Both apparently healthy and seriously ill piglets can be born, dying in the first days of life. Tremors can range from mild shaking movements of the head and limbs to severe shaking throughout the body [22, 24]. Sick animals are unable to move independently and suck colostrum, despite the strong manifestation of the sucking reflex, so most die of starvation [56]. In some cases, young animals are born with anatomical abnormalities of the limbs. There may also be temporary dysfunction of the hind limbs, which occurs soon after birth and leads to difficulty walking. The survival rate of piglets born with CT is significantly reduced, but still depends on the conditions of detention and care. Over time, CT signs disappear completely [24, 52, 56]. A. Postel et al. [56] reported that, unlike other pestiviruses, APS most often accumulates in the inner layer of cerebellar granule cells of infected animals. This may explain the resolution of the CT sign over time, since the loss of inner granule cells can be compensated for by migration of cells from the outer granule cell layer during the first weeks after birth [56].

In piglets with CT, the virus can be detected in all organs, feces, saliva, blood serum [24, 31, 32, 35, 36], as well as in the central nervous system (cerebellum) and lymphoid tissue (inguinal, submandibular lymph nodes) [24, 36, 56]. It is assumed that the use of infected semen during artificial insemination leads to the birth of infected offspring, since boars already at the age of 6 months spread the virus through seminal fluid [24, 31, 33]. In utero infected piglets can become persistently infected and spread the virus throughout their lives [31, 35]. However, these mechanisms are not well understood.

Postmortem examination of naturally infected piglets with type A-II CT revealed varying degrees of brain hypomyelination, and a moderate decrease in the amount of myelin was observed in the spinal cord [56].

Diagnostics and prevention. *Methods.* Diagnosis of infection caused by APS involves the use of a set of methods. The primary diagnosis is made when symptoms of congenital tremor appear in piglets of any age. The absence of obvious clinical signs does not serve as a basis for establishing a negative farm status for this infection. For diagnosis, molecular genetic, virological and serological research methods are used.

The use of metagenomic sequencing in veterinary practice has made it possible to identify APS in a number of countries [23, 31, 32]. Based on the study of various regions of the virus genome, several systems for PCR analysis have been developed (quantitative real-time PCR, multiplex PCR test system, semi-quantitative duplex RT-PCR analysis, etc.) [34, 35, 39, 41].

APS were isolated in cell cultures of various species of origin [23, 60, 62]; clinical and pathological material from infected, suspected of infection, and forcedly killed animals were used as a source of the virus. For the first time M. Beer et al. [58] were able to isolate a non-cytopathogenic virus in a culture of pig embryonic kidney cells (SPEV, swine embryo kidney). Virus replication in cell culture was confirmed by RT-PCR and high-throughput sequencing [58]. Research by L. Schwarz et al. [35] showed that APS also multiplies (albeit at low titers) in continuous cell cultures of pig kidneys PK-15 (porcine kidney) and SK-6 (swine kidney). The presence of noncytopathogenic virus was determined by

immunofluorescence and PCR methods [35].

Enzyme immunoassay allows one to reliably and with high sensitivity diagnose APS infection. Various ELISA test systems have been developed based on the NS3, E2 and Erns proteins [35, 47, 57, 62], which can be used to conduct regular serological monitoring in different age groups of pigs. Immunohistochemistry, in situ hybridization [36, 56], neutralization reaction, and immunofluorescence are also widely used to diagnose infection [57, 85, 86].

Differential diagnosis. Based on the history, clinical picture and observed pathological changes, it is necessary to first exclude classical swine fever, since infection of pregnant sows with a low-virulent strain of the CSF virus leads to the birth of piglets with congenital tremor (87). APS must be differentiated from *Linda virus*, *Pestvirus F*, *Porcine teschovirus* (PTV), *Porcine astrovirus* (PAstV) and porcine circoviruses, which can also cause neurological disorders in pigs. Treatment of animals infected with APS has not been reported.

Prevention and control. Currently, no vaccine has been developed to prevent infection caused by APS in pigs. Two vaccines have been reported and are effective in preventing infection in BALB/c mice [77, 79]. As with other viral infections, it is important to prevent the pathogen from being introduced into the herd. Animals entering the herd must be quarantined and tested for the presence of pestiviruses. It is also necessary to examine boar sperm used for artificial insemination for the presence of APS, since it can serve as a source of infection for sows.

So, today atypical porcine pestivirus (APV) is widespread in Europe and Asia. APS infection in pigs is mainly associated with symptoms of congenital tremor (CT). Taking into account the fact that CT symptoms in pigs were described long before the identification of APS, it can be assumed that the virus has been circulating in pig herds for several decades. The use of next-generation sequencing in veterinary practice has made it possible to identify not only APS, but also completely new pestiviruses in both pigs and other animal species. The circulation of new pestiviruses in domestic and wild pig populations may affect the effectiveness of anti-epizootic measures against known pestiviruses, such as classical swine fever and bovine viral diarrhea viruses. It is necessary to constantly monitor the epizootic situation and improve test systems to identify these pathogens and carry out differential diagnosis. To date, information has already been accumulated on the genetic diversity of APS, but the antigenic structure of some proteins of this virus has not been sufficiently studied. An analysis of literature data showed that antibodies to the E2, Erns and NS3 proteins are detected in the body of pigs infected with an atypical pestivirus. In response to E2 and Erns, the largest number of virus-neutralizing antibodies are formed both in naturally infected pigs and in experimentally vaccinated laboratory animals. Glycoprotein E2 of APS is considered immunodominant, since it has antigenic determinants (epitopes) that are recognized in the cellular and humoral immune response to the virus. Therefore, it is necessary to study the antigenic structure of E2 in APS, since this protein can be used as an antigenic marker in the creation of a subunit vaccine against APS for pigs. In addition, to understand the peculiarities of the interaction of APS with the pig immune system, an analysis of epitopes of the E2 protein is necessary. The available data on cross-protection between APS and other pestviruses is also insufficient. The wide distribution of APS in different countries requires studying the ecology, pathogenesis, transmission routes, and persistence of the virus in the host body. There is insufficient knowledge about the role of feral pigs in the spread of APS. In addition, it is important to evaluate the impact of this virus on pig productivity.

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