Congenital abnormalities in calves associated with Peaton virus infection in Japan

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Abstract. Peaton virus (PEAV; family *Peribunyaviridae*, genus *Orthobunyavirus*) appears to be capable of producing congenital malformations in ruminants; however, its pathogenicity remains unknown given its relatively low incidence. We evaluated the relationship between congenital abnormalities of calves and PEAV infection by serologic, epidemiologic, pathologic, and virologic investigations using specimens from 31 malformed calves in the years 1996–2016 in Japan. Antibody testing was carried out for known teratogenic viruses, including Akabane, Aino, Chuzan, and bovine viral diarrhea viruses, in the precolostral sera of these abnormal calves, but all results were negative. However, all 31 malformed calves were positive for antibodies against PEAV. A PEAV-specific gene was amplified from central nervous system tissues from a stillborn calf delivered in April 2007, and its nucleotide sequence was identical with that of PEAV isolated from healthy sentinel cattle in September 2006. These findings indicate that PEAV can cause bovine congenital anomalies.

Key words: Arbovirus; arthropod-borne; bunyavirus; cattle; congenital malformation.

Introduction

Fetal death and congenital malformations caused by arthropod-borne viruses (arboviruses), such as Akabane virus (AKAV, species *Akabane orthobunyavirus*) and Aino virus (AINOV, species *Shuni orthobunyavirus*; order Bunyavirales, family *Peribunyaviridae*, genus *Orthobunyavirus*) occasionally have impeded the production of ruminant livestock in the temperate zones of Asia, the Middle East, and Australia.[4,5,9,16,29] AKAV and AINOV have been experimentally verified as teratogenic pathogens in ruminants.[18,19,24,31] Studies on field clinical cases have indicated the teratogenicity of other orthobunyaviruses, such as Schmallenberg virus (SBV) and Shamonda virus (SHAV, species *Shamonda orthobunyavirus*), in domestic ruminants. An epidemic in 2011–2013 of fetal deformities caused by SBV resulted in large economic losses in the European livestock industry.[1] Naturally occurring intrauterine SHAV infections were likely involved in bovine congenital malformations in an epizootic in Japan in 2015–2016.[11] Based on complement fixation testing, the above-mentioned orthobunyaviruses have been included in the Simbu serogroup.[15] Although this serologic classification has not been certified by the International Committee on Taxonomy of Viruses (ICTV), the designation "Simbu serogroup" is often used for convenience. The relation of SBV to this serogroup was also indicated by phylogenetic studies.[10,12]

Peaton virus (PEAV) was initially isolated from *Culicoides brevitarsis* and bovine blood in Australia in the 1970s and has been recognized as a member of the Simbu serogroup.[28] In the 2017 ICTV classification, PEAV is regarded as a variant of species *Shamonda orthobunyavirus*.[8] However, genetic analyses showed that SHAV and PEAV are remotely related and thus reclassification is needed.[10,35] As in other orthobunyaviruses, PEAV possesses 3 distinct linear, negative-stranded RNA segments: the S RNA segment encodes the nucleocapsid protein and a nonstructural protein (NSs); the M RNA segment encodes the precursor polyprotein, which is cleaved to form 2 viral surface glycoproteins Gc

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and Gn, and a nonstructural protein NSm; and the L RNA segment encodes the RNA-dependent RNA polymerase.[8,10,36] Experimental infection of a pregnant ewe with PEAV induced congenital defects in its lamb.[25] However, the etiologic role of PEAV in nature has not yet been evaluated, to our knowledge. PEAV has been isolated repeatedly from *Culicoides* biting midges and sentinel calves since 1987 in southern Japan.[34] After the spread of PEAV, antibodies against PEAV were detected from calves with arthrogryposis and gross anatomic lesions in the central nervous system (CNS), suggesting its teratogenicity to fetal calves.[21] We examined the possible role of PEAV in congenital abnormalities of calves using clinical samples.

Materials and methods

Abnormal calves

Thirty-one newborn calves with abnormalities consistent with an arbovirus infection, but neither AKAV nor AINOV, were subjected to serologic, epidemiologic, pathologic, and virologic examinations (Table 1). Virus neutralization (VN) titers ≥2 from malformed calves were considered positive for neutralizing antibody to the virus.

Virus neutralization test

Precolostral sera and/or body fluids from abnormal calves and their dams were examined by a VN test using bovine arboviruses (AKAV, AINOV, PEAV, Chuzan, and Ibaraki) and bovine viral diarrhea virus (BVDV). Ascites, pleural effusion, and/or cerebrospinal fluid were used in some cases when it was difficult to collect blood samples from stillborn calves. Sera of naive calves with no previous exposure to PEAV were used as the sentinel control group and were collected 4 or 5 times between June and November. Specimens inactivated at 56°C for 30 min were serially diluted 2-fold with serum-free Eagle minimum essential medium (MEM; Nissui Pharmaceutical, Tokyo, Japan) in 96-well cell culture microplates. Each serum dilution was mixed with an equal volume of 100 $TCID_{50}$ of virus and incubated at 37°C for 1 h. Then, hamster lung (HmLu-1) cells suspended in GIT medium (Wako Pure Chemical Industries, Osaka, Japan) were added to each well. After incubation at 37°C for 7 d, the antibody titer was determined as the reciprocal of the highest serum dilution showing 50% inhibition of the cytopathic effect (CPE).

Processing of tissues for histopathology and immunohistochemistry

Tissue samples of the CNS, skeletal muscle, and other organs were collected from the abnormal calves. The samples were fixed with 10% buffered formalin, processed routinely, and stained with hematoxylin and eosin for histologic examination. One pair of serial sections was submitted for immunohistochemical detection of PEAV antigens. After deparaffinization of the paired sections, endogenous peroxidase activity was inhibited by treatment with 3% H_2O_2 in absolute methanol for 20 min at room temperature. In each section pair, one section was incubated with a diluted rabbit antiserum (1:2,000) against the PEAV NS-3/P/99 strain,[21] whereas the other was not, serving as the negative control. The sections were then labeled (HISTOFINE SAB-PO kit, Nichirei, Tokyo, Japan) with a biotinylated secondary antibody for anti-rabbit IgG and streptavidin-conjugated peroxidase. Localized peroxidase conjugates were visualized with 3,3'-diaminobenzidine. Sections were counterstained with hematoxylin.

RNA extraction and detection of viral genome

Tissue specimens obtained from the brain and spinal cord of abnormal calves were rinsed, minced, and homogenized in serum-free MEM. The supernatant of a 10% homogenate of each tissue was used for viral RNA preparation. Total RNA was extracted (QIAamp viral RNA mini kit, Qiagen, Hilden, Germany). Primer pair AKAI172F/AKAI560R (5'-CAGAAGAAGGCCAAGATGGT-3'/5'-AAGTT GACATCCATTCCATC-3') and a RT-PCR kit (OneStep, Qiagen) were used to detect the viral S RNA segment. Reverse transcription was conducted at 50°C for 30 min. This mixture was then heated at 95°C for 15 min to stop the reaction and to activate HotStart *Taq* DNA polymerase (Qiagen). The resulting complementary DNA was amplified by 35 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 30 s and extension at 72°C for 45 s, followed by one step of final extension at 72°C for 10 min. PCR products were electrophoresed on 1.5% agarose gel and visualized by staining with ethidium bromide.

Sequence analysis of the PCR products

Cerebrum and spinal cord tissues of a stillborn calf (case 11) were positive by the RT-PCR assay. The obtained PCR fragments were purified (QIAquick PCR purification kit, Qiagen) and directly sequenced in both orientations with primers AKAI206F (5'-CACAACCAAGTGTCGATCTTAC-3') and AKAI560R (BigDye terminator v.3.1 sequencing kit, ABI3100-Avanti genetic analyzer, Thermo Fisher Scientific, Waltham, MA). Nucleotide sequences were analyzed (DNA-SIS Pro v.2.0, Hitachi Software Engineering, Tokyo, Japan; University of Wisconsin Genetic Computer Group (UWGCG) software package, Pharmacopeia, Princeton, NJ). Nucleotide sequence data were deposited in the DNA Data Bank of Japan under accession AB568273.

Virus isolation

The supernatant of homogenized tissues described above was also used for virus isolation. In addition, blood samples were collected from sentinel calves distributed throughout

Table 1. Characteristics of bovine congenital anomalies associated with Peaton virus in Japan, 1996–2016.

Case	Date of occurrence (y/mo/d)	Geographic origin	Breed	Clinical signs, pathologic findings	VN titer* Case	VN titer* Dam
1	1996-01-11	Nagasaki	Japanese Black	Premature birth, arthrogryposis, spinal curvature, cerebellar hypoplasia	16	64
2	1996-02-02	Nagasaki	Japanese Black × Japanese Brown	Weakness, blindness, arthrogryposis, spinal curvature	64	32
3	1996-02-19	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, cerebellar hypoplasia	32	32
4	1996-02-27	Nagasaki	Japanese Black	Stillbirth, spinal curvature, hydrocephalus	16	8
5	2000-03-07	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, hydrocephalus	32	64
6	2000-04-03	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, hydrocephalus	8	64
7	2004-03-01	Yamaguchi	Japanese Black	Stillbirth, spinal curvature, cranial deformity, cerebellar hypoplasia, hydrocephalus	16	16
8	2005-10-03	Okinawa (Ishigaki Island)	Japanese Black	Stillbirth, arthrogryposis, spinal curvature	128	≥256
9	2005-11-06	Okinawa (Ishigaki Island)	Japanese Black	Premature birth, arthrogryposis, spinal curvature, hydrocephalus, cerebellar hypoplasia	16	64
10	2005-11-09	Okinawa (Ishigaki Island)	Japanese Black	Blindness, arthrogryposis, malformed feet	64	128
11**	2007-04-02	Tottori	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, hydrocephalus	4	16
12	2007-04-10	Kagoshima	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, cranial deformity, cerebellar hypoplasia	16	64
13	2007-04-13	Kagoshima	Japanese Black	Stillbirth, arthrogryposis, spinal curvature	8	64
14	2007-07-22	Okinawa (Okinawa Island)	Japanese Black	Stillbirth, arthrogryposis, spinal curvature	32	64
15	2007-11-19	Nagasaki	Japanese Black	Arthrogryposis, spinal curvature, hydrocephalus	≥256	128
16	2007-12-12	Nagasaki	Japanese Black	Ataxia, blindness, hydrocephalus	64	128
17	2007-12-20	Okinawa (Okinawa Island)	Japanese Black	Stillbirth, arthrogryposis, spinal curvature	16	128
18	2008-01-15	Nagasaki	Japanese Black	Stillbirth, spinal curvature, cerebellar hypoplasia, hydrocephalus	4	≥256
19	2008-01-28	Nagasaki	Japanese Black	Arthrogryposis, spinal curvature	64	≥256
20	2008-01-31	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, cranial deformity	≥256	≥256
21	2008-02-02	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, hypoplasia of coxa	32	128
22	2008-02-11	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature	64	128
23	2008-02-26	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, cranial deformity	16	128
24	2008-02-29	Kumamoto	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, hydrocephalus	8	64
25	2008-03-08	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, hydrocephalus	≥256	≥256
26	2008-03-14	Kumamoto	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, cerebellar hypoplasia	2	32
27	2011-01-17	Kagoshima	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, cranial deformity, hydrocephalus	32	64
28	2011-02-14	Kagoshima	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, cranial deformity	16	32
29	2011-02-27	Kagoshima	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, cranial deformity, cerebellar hypoplasia	4	256
30	2011-03-14	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature	16	≥256
31	2016-03-04	Nagasaki	Japanese Black	Stillbirth, arthrogryposis, spinal curvature, hydrocephalus, cerebellar hypoplasia	64	≥256

* Titers ≥2 for malformed cattle were considered positive for neutralizing antibody to Peaton virus.
** The dam was introduced from Kagoshima to Tottori Prefecture on January 21, 2007; Peaton viral RNA was detected from the stillborn calf.

Nagasaki, Kagoshima, and Okinawa Prefectures. Heparinized blood samples were separated into erythrocytes and plasma by centrifugation, and erythrocytes were washed 3 times with ice-cold phosphate-buffered saline. The supernatants of 10% homogenates of tissues, plasma, and washed erythrocytes were stored at −80°C until use. These specimens were inoculated into monolayer cultures of HmLu-1 and/or baby hamster kidney (BHK-21) cells. After incubation at 37°C for 7 d, cell culture fluids were pooled and subinoculated into freshly prepared cell cultures at least twice until the infected cells exhibited CPE. The isolated viruses were identified by immunobinding assay as described previously using monoclonal antibodies recognizing the Gc protein of PEAV.[17,37]

Results

Clinical, pathologic, and epidemiologic features

Characteristic arthrogryposis and/or spinal curvature was consistently observed in 30 of 31 affected calves (Table 1, Fig. 1). Hydrocephalus (13 of 31) and cerebellar hypoplasia (9 of 31) were seen occasionally. However, hydranencephaly, as found in clinical cases of AKAV and AINOV infections, was not detected in the affected calves. Histologic examination indicated atrophy, dysplasia, and loss of skeletal muscle fibers accompanied by adipose replacement without polymyositis (18 of 30; Fig. 2), and loss of neurons in the ventral horn of the spinal cord (15 of 30) in many cases (Fig. 3). Nonsuppurative encephalomyelitis was recognized in only one case (11). No obvious changes to other main organs were observed in any of the cases.

Thirty-one abnormal calves, of which 24 were stillbirths at the end of gestation, possessed antibodies specific to PEAV (Table 1). No antibodies against other arboviruses were detected in any affected calves. Antibodies to BVDV were found in an affected calf, but the VN titer was very low (≤4). All dams also possessed neutralizing antibodies against PEAV, but had not shown any clinical signs. These cases of congenital abnormalities occurred between July and the following April in 1996–2016 in 6 prefectures (Nagasaki, Okinawa, Kumamoto, Kagoshima, Yamaguchi, and Tottori) in southwestern Japan. Of 31 calves, 24 were found in Kyushu district (the westernmost area of the mainland) and 5 in Okinawa Prefecture (the southernmost area consisting of many small islands). Twelve abnormal calves were delivered between November 2007 and March 2008.

Detection of viral antigens and genes, and virus isolation from clinical samples

Despite several attempts, no PEAV antigen was detected in the tissue samples from lesions in the CNS or skeletal muscles of the affected calves. No viruses were isolated. However, the viral gene (expected size of 389 bp) was amplified
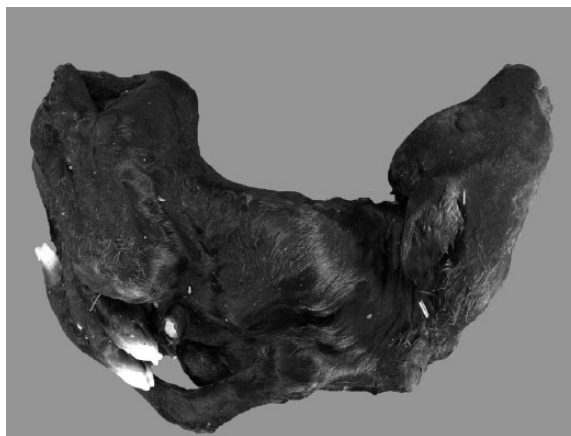

Figure 1. A Peaton virus–infected calf with arthrogryposis and spinal curvature (case 25).
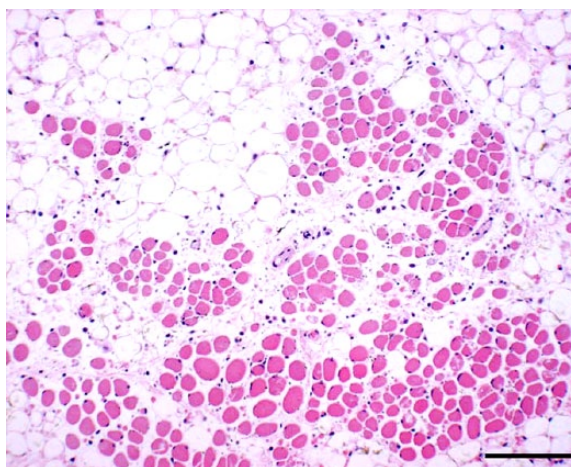

Figure 2. Atrophy, dysplasia, and loss of skeletal muscle fibers accompanied by adipose replacement attributed to Peaton virus infection in a stillborn calf. H&E. Bar = 0.25 mm.
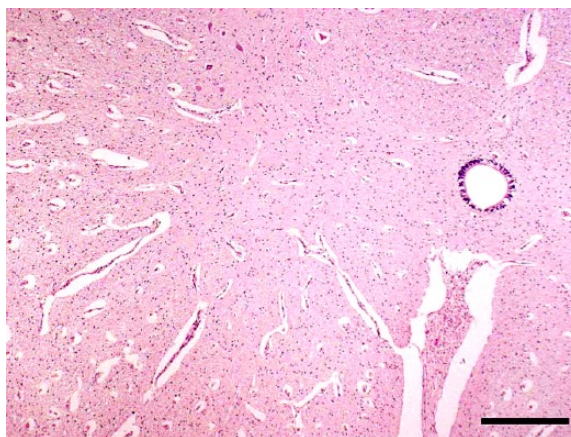

Figure 3. Loss of neurons in the ventral horn of the spinal cord of a Peaton virus–infected stillborn calf. H&E. Bar = 1 mm.

from the brain and spinal cord tissue of a stillborn calf (case 11) delivered in April 2007 in Tottori Prefecture (Table 1).

Sequence analysis of the PCR products

Except for the primer-binding sites, the nucleotide sequence of the amplified gene from case 11 was determined and compared with the corresponding region of the genomic sequences of PEAV strains reported previously.[21,34] The PCR fragment showed identities of 90.4%, 99.0%, and 99.7% with positions at nucleotides 211–523 in the S RNA segment of the CSIRO110, NS-3/P/99, and MZ-4/C/99 strains, respectively, and was identical with that of the KSB-1/P/06 strain isolated in September 2006 in Kagoshima Prefecture (Supplementary Table 1).

Virologic and serologic analyses of sentinel calves

Ten strains of PEAV were isolated from bovine blood samples collected in Okinawa (1987, 2001, 2005, and 2009), Nagasaki (1999), and Kagoshima (2006 and 2010) Prefectures (Supplementary Table 1). Two strains of the virus were also obtained from *Culicoides* biting midges captured at cowsheds in Miyazaki in 1999 and Kagoshima in 2010.[13,21]

Retrospective serologic investigation using the sera of sentinel calves collected in 1985–2009 in Nagasaki Prefecture (71–75 per year) revealed that seroconversion to PEAV occurred 6 times, or once each in 1985 (positive rate: 2%), 1987 (8%), 1995 (11%), 1999 (38%), 2007 (27%), and 2009 (7%). In the spring of the years after high seroconversion rates were observed, the numbers of abnormal calves suspected of PEAV infection were 4 (1996), 2 (2000), and 7 (2008; Table 1). In Okinawa Prefecture, seroconversion was frequently observed in sentinel calves in 1996–2009. PEAV seemed to have circulated in this area during each of 6 different years: 1996 (positive rate: 4%), 1998 (3%), 1999 (3%), 2005 (5%), 2007 (11%), and 2009 (4%). During this period, however, only 5 suspected cases were reported in Okinawa Prefecture (Table 1).

Discussion

Detection of virus-specific antibodies in the precolostral serum of abnormal offspring can be useful to identify etiologic agents. In general, only transient viremia of the related orthobunyaviruses has been observed in infected animals.[19,33] Therefore, virus isolation and viral gene detection are generally unsuccessful in malformed calves, because the virus disappears from the infected fetuses during gestation.[6] Surveillance in sentinel animals is useful to detect new or unexpected arboviral disease.[11,23,27,30] The detection of specific antibodies in 31 malformed calves and viral circulation in the affected regions strongly suggested an association between PEAV and the congenital abnormalities. Although

signs and pathologic findings were very similar to other cases, antibody titers in body fluids from several affected calves (cases 18, 26, and 29) were low. Because VN tests for Simbu serogroup viruses often produce nonspecific reactions,[20] more evidence of in utero infection is needed to support the involvement of PEAV in these cases. The amplification of a PEAV-specific gene from affected calf 11 supported our suspicion. Of interest is that the sequence of the amplified product was identical with the corresponding region of the PEAV KSB-1/P/06 strain isolated in Kagoshima in the autumn of 2006. The dam of case 11 was transported from Kagoshima to Tottori in the winter of 2007, suggesting that the infection occurred in Kagoshima. Serosurveillance and virus isolation from sentinel cattle indicated that almost all of the other clinical cases were epidemiologically consistent with the circulation of PEAV.

The clinical and pathologic features of malformed calves associated with PEAV resembled those caused by AKAV and AINOV. Arthrogryposis and spinal cord lesions were frequently found in the malformed calves confirmed to have PEAV infection. However, the brain lesions of the PEAV-infected calves appeared to be milder than those in calves infected with AKAV or AINOV. Also, fatty replacement in skeletal muscle was an observation specific to PEAV. These findings suggest that the tissue tropism and pathogenic capacities of PEAV are different than those of AKAV and AINOV. On the other hand, fatty replacement in skeletal muscle has been observed in malformed calves affected by SBV and SHAV.[2,11,26] Comparison of the lesions caused by these orthobunyaviruses will clarify tissue tropism and lesion pathogenesis in malformed calves. There were no reports of bovine abortions associated with PEAV during the study period.

Until vaccines were used more widely, large outbreaks of congenital abnormalities caused by AKAV and AINOV occurred repeatedly.[9] During the largest epidemic caused by AKAV (1972–1975), 42,000 affected calves were reported throughout Japan. AINOV was also involved in at least 700 cases of fetal death and congenital abnormalities in cattle in 1995–1996. However, reported cases of bovine malformation associated with PEAV were highly sporadic (1–12 cases in each epidemic season). Insufficient awareness and motivation to report might have affected these data. However, no obvious increase of bovine congenital abnormalities was reported after PEAV spread in the endemic regions (data not shown). These findings imply that the pathogenicity of PEAV is relatively low in comparison with that of AKAV and AINOV. As of 2018, it seems that PEAV has a low or limited impact on cattle reproduction in Japan. Although vaccination is an effective measure to prevent fetal death and congenital abnormalities caused by orthobunyaviruses, its application to PEAV must be carefully considered from a cost-effectiveness perspective.

Serosurveys have indicated that PEAV is widely distributed in Africa, Asia, and Australia.[20,22,28,32] Although PEAV

potentially affects reproductive performance in domestic ruminants, no association between reproductive disorders and PEAV has been reported from its regions of prevalence outside Japan. This could be explained by a lack of prevalence data for this agent and/or reporting systems. In some regions, animals may be infected and develop immunity to PEAV before reaching reproductive age. If the virus is introduced into a nonendemic region, outbreaks of malformation will be more obvious. High seroprevalence (58–71%) against PEAV was observed in lower-latitude areas, such as in Indonesia and Tanzania,[20,22] suggesting that the virus exists in tropical and/or subtropical zones. It has been postulated that long-distance movement of *Culicoides* biting midges is associated with the spread of arboviruses.[7] Antibodies against PEAV in sentinel cattle have been detected frequently in the most-southwestern islands of Japan during long-term monitoring, suggesting that PEAV has been endemic in neighboring subtropical regions.[14] The abnormal calves confirmed to be infected with PEAV were localized to western Japan, which suggests that the infected midges may have been brought by air streams from overseas.

If PEAV is introduced into a large naive ruminant population, the impact will become more significant. The large outbreak of abnormal deliveries in previously SBV-free regions suggests this possibility.[1] Several possible reassortants between closely related orthobunyaviruses were identified by genetic analyses of field-isolated viruses, and such reassortants had features distinct from those of their parent viruses.[3] Genetic reassortment between PEAV and other orthobunyaviruses could possibly change viral antigenicity and pathogenicity. A previous phylogenetic study indicated that a reassortment occurred between AINOV and PEAV in nature.[34]

Our findings did not show high animal losses caused by PEAV infection. However, a differential diagnosis of congenital abnormalities caused by orthobunyaviruses including AKAV, AINOV, SHAV, and PEAV would be necessary in regions where these viruses are co-distributed. We recommend that PEAV be added to the list of possible etiologic agents that can be found in malformed calves. Further work to clarify differences in pathogenicity among Simbu serogroup viruses will contribute to the development of strategies to prevent and reduce animal losses caused by these potentially teratogenic viruses.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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