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RESEARCH ARTICLE

Congenital cerebral and cerebellar anomalies in relation to bovine viral diarrhoea virus and Akabane virus in newborn calves

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ABSTRACT

Congenital malformations occur sporadically in cattle; however, congenital structural and functional disorders of the nervous system are rather common in ruminants. Among the numerous causes of congenital nervous system defects, infectious agents are highlighted in this paper. Virus-induced congenital malformations are well known, among which those caused by bovine viral diarrhoea virus (BVDV), Akabane virus (AKAV), Schmallenberg virus (SBV), Bluetongue virus (BTV), and Aino virus (AV) are the most studied. In this study, we specify and categorise macroscopic and histopathological lesions in the brain of 42 newborn calves suffering from severe neurologic signs and diagnosed with BVDV and AKAV infection. Following a complete necropsy, specimens were collected from the brains to track the presence of BVDV, AKAV and SBV utilising reverse transcription polymerase chain reaction. Of the 42 examined calves, 21 were BVDV positive and 6 were AKAV positive, while 15 brains were negative for the studied agents. Regardless of the aetiology, cerebellar hypoplasia, hydranencephaly, hydrocephalus, porencephaly, and microencephaly were detected. Cerebellar hypoplasia was the most common lesion seen in both BVDV-positive and AKAV-positive cases. Virus-induced necrosis of the germinative cells of the external granular layer of cerebellum, as well as vascular damages, are believed to be the underlying causes of cerebellar hypoplasia. BVDV was the most important aetiological agent of such cases in this study.

KEYWORDS

BVDV, AKAV, central nervous system anomalies, cerebellar hypoplasia, calf

INTRODUCTION

Congenital malformations occur sporadically in cattle, although the number may rise in some herds over time. Among all congenital abnormalities, central nervous system (CNS) and musculoskeletal defects are easily diagnosed by clinical examination (Agerholm et al., 2015). Congenital structural and functional disorders of the nervous system are rather common in ruminants. The significant susceptibility to developmental anomalies is associated with the 'high degree of differentiation and complexity' of this system (Washburn and Streeter, 2004). Among the numerous causes of congenital nervous system defects, hereditary defects,

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nutritional deficiencies, enzyme deficiencies, and infectious and toxic environmental agents are the most highlighted (Washburn and Streeter, 2004; Queiroz et al., 2013). Today, virus-induced congenital malformations of the CNS are well known and the contributing viral agents have been detected in several countries. Bovine viral diarrhoea virus (BVDV), Akabane virus (AKAV), Schmallenberg virus (SBV), Bluetongue virus (BTV), and Aino virus (AV) are the most studied teratogenic viral agents to cause CNS malformations, especially in the brain following intrauterine infection (Vercauteren et al., 2008; Agerholm et al., 2015; Collins et al., 2019; Di Muro et al., 2020; Malik et al., 2020; Romero et al., 2020). Thus, the presented cases were studied for BVDV, AKAV, and SBV.

Bovine viral diarrhoea virus, a pestivirus of the family *Flaviviridae*, is a single-stranded, enveloped, positive-sense RNA virus, capable of causing a range of congenital malformations and serious clinical disease in the bovine population, as it is a teratogenic agent. Two genotypes of the virus have been recognised, BVDV-1 and BVDV-2. Recently, a third genotype has been proposed as BVDV-3, HoBi-like pestivirus (HoBiPeV) or pestivirus H (Shi et al., 2016; Silveira et al., 2018; Silveira et al., 2020). Within each genotype, noncytopathic (NCP) and cytopathic (CP) biotypes are defined, based on their cytopathic effects on cell culture, and variations in the manifestation of BVDV-induced disease (Montgomery, 2007; Montgomery et al., 2008; Porter et al., 2010; Lanyon et al., 2014; Agerholm et al., 2015). BVD is one of the most prevalent infectious diseases in cattle (Lanyon et al., 2014). Additionally, the infection causes morbidity, mortality, and imposes massive health and economic burden on the cattle industry worldwide, stemming primarily from its reproductive and immunosuppressive effects (Montgomery, 2007; Montgomery et al., 2008; Atmaca et al., 2012; Queiroz et al., 2013; Lanyon et al., 2014). Transplacental fetal infection with NCP BVDV during the first 4 months of gestation leads to the most serious consequences, including early embryonic death, fetal resorption, mummification, abortion, development of congenital abnormalities and, if the fetus survives, a persistently infected (PI) calf will be born. Intrauterine infection between 90 and 120 days of gestation results in a wide spectrum of teratogenic lesions. The most prominent are developmental malformations in the CNS, especially the brain, including microencephaly, hypomyelinogenesis, cerebellar atrophy, hypoplasia and dysgenesis, hydranencephaly, hydrocephalus, pseudocyst formation in the brain, and defective myelination of the spinal cord. It can be concluded that the brain is the primary target in persistent infection. Even in the absence of neurological clinical signs BVDV antigen can be detected, by means of immunohistochemistry, in a variety of cell types including neurons, astrocytes, oligodendrocytes, and germinative cells present in the leptomeninges (Tunca et al., 2006; Montgomery, 2007; Montgomery et al., 2008; Queiroz et al., 2013; Lanyon et al., 2014; Agerholm et al., 2015; Cantile and Youssef, 2016). It is worthwhile to mention that brain lesions have only been demonstrated in PI calves, and not in transiently infected ones (Montgomery et al., 2008).

Akabane virus, an orthobunyavirus of the *Peribunyaviridae* family in the Simbu serogroup, causes an arthropod-borne syndrome, first detected in 1974. Abortion, premature birth, stillbirth, arthrogryposis, hydranencephaly, microencephaly and polioencephalomyelitis are the most highlighted features of AKAV infection (Umemura et al., 1987; Haligur et al., 2014; Agerholm et al., 2015; Oğuzoğlu, 2018; Di Muro et al., 2020). AKAV is known as one of the most potent viral teratogens of cattle, sheep and goats (Agerholm et al., 2015; Oğuzoğlu, 2018). In cattle, the susceptibility window is believed to be between 80 and 150 days of gestation (Oğuzoğlu, 2018), although previous studies have claimed it to also include 29–48 (Haligur et al., 2014), 79–104 and 103–174 days of gestation (Agerholm et al., 2015). Nested RT-PCR is a reliable technique for the detection of AKAV (Oğuzoğlu, 2018).

Schmallenberg virus, also an orthobunyavirus of the *Peribunyaviridae* family in the Simbu serogroup, is an arthropod-borne agent with three genomic ssRNA segments. SBV was first detected in Europe in 2011 as a novel and emerging pathogen, and an economically important teratogen affecting domestic and wild ruminants. Infection in adult cattle causes mild, if any, clinical signs including diarrhoea, transient pyrexia, anorexia, and reduced milk production. During the susceptibility window (gestation days between 60 and 180), intrauterine infection with SBV leads to abortion, stillbirth, or nervous and musculoskeletal malformations, especially arthrogryposis and hydranencephaly. In addition, inflammatory responses may also develop. Real-time PCR, virus isolation and antibody ELISA are reliable diagnostic techniques (Beer et al., 2013; Conraths et al., 2013; Doceul et al., 2013; Wernike et al., 2013, 2014, 2015; Agerholm et al., 2015; Claine et al., 2015; Lievaart-Peterson et al., 2015; Peperkamp et al., 2015; Collins et al., 2019; Endalew et al., 2019; Di Muro et al., 2020; Malik et al., 2020). In contrast to cattle, sheep and goats commonly experience a mild clinical course of the disease (Doceul et al., 2013; Hahn et al., 2013).

The purpose of this study is to specify and categorise the macroscopic and histopathological lesions in the brain of newborn calves suffering from severe neurological signs and diagnosed with BVDV and AKAV infection. Virus detection was based on RT-PCR examination.

MATERIALS AND METHODS

In the period of 2015–2016, 42 newborn calves presenting severe neurological signs, were referred to Mabna veterinary diagnostic laboratory from farms located in Alborz province. Ensuring animal ethics, following euthanasia, necropsy was performed. Brains were carefully removed and investigated pathomorphologically.

Polymerase chain reaction

Specimens were collected from the brains in order to track the presence of BVDV, AKAV and SBV utilising reverse

transcription polymerase chain reaction (RT-PCR, nested RT-PCR and RT-PCR, respectively). RNA extraction was carried out using a commercial kit (MBST, Tehran, Iran), and it was isolated according to the manufacturer's recommendation. OneStep RT-PCR Kit (QIAGEN, Germany) was used for the RT-PCR procedure. DNA Taq polymerase Master Mix (Ampliqon, Denmark) was utilised for the following steps of nested RT-PCR. Primers used in this procedure are listed in Table 1. The PCR products were loaded on 1% agarose gel and stained with a safe stain. Following the electrophoresis, the gel was photographed under ultraviolet light and the obtained results were compared to the negative and positive controls (Fig. 1).

Histopathology

The whole brains were immersed in 10% neutral buffered formalin. After the 5- to 10-day fixation period, specimens were obtained from the cerebrum, hippocampus, anterior colliculus, cerebellum, medulla at the level of obex, and caudal medulla. Tissue processing and paraffin embedding were followed by sectioning at 5-µm thickness and routine haematoxylin and eosin (HE) staining. Slides were examined by light microscope, and compared with tissues obtained from normal healthy calves of the same age. A normal cerebellar fold is depicted in Fig. 2.

Table 1. Sequence of the primers used in the present study

Pathogen	Forward/ Reverse Primer	Primer sequence
BVDV	F	GTAGTCGTCAGTGGTTCG
BVDV	R	GCCATGTACAGCAGAGAT
AKAV	F1	TAACTACGCATTGCAATGGC
AKAV	R1	TAAGCTTAGATCTGGATACC
AKAV	F2	GAAGGCCAAGATGGTCTTAC
AKAV	R2	GGCATCACAATTGTGGCAGC
SBV	F	GTGCTCCACTATTAACTACAGAAA
SBV	R	AGAAGCCTTGCAGTATAATGGTG

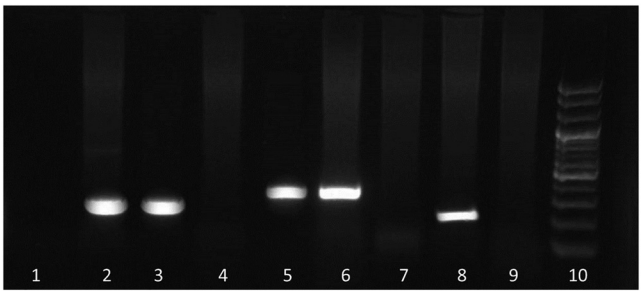

Fig. 1. Post-electrophoresis gel image. Electrophoresis results from left to the right: 1) Akabane-negative control, 2) Akabane-positive control, 3) Akabane sample, 4) BVDV-negative control, 5) BVDV-positive control, 6) BVDV sample, 7) Schmallenberg-negative control, 8) Schmallenberg-positive control, 9) Schmallenberg sample, 10) Molecular marker, 100 bp

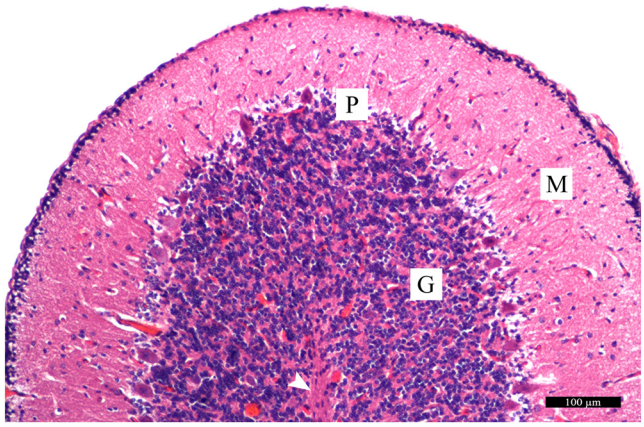

Fig. 2. Calf. Normal cerebellum. Molecular (M), Purkinje (P), and granular (G) cell layers of grey matter are present, associated with white matter (arrowhead). Microphotograph, haematoxylin-eosin (HE). Bar = 100 µm

RESULTS

The studied calves suffered from circling, blindness, ataxia, nystagmus, and depression. Among the 42 examined patients, 21 were BVDV positive, 6 were AKAV positive, and in 15 brains none of the studied viral agents, including SBV, were detected. Of all investigated calves, cerebellar hypoplasia was the most frequently noted macroscopic abnormality, followed by hydranencephaly, hydrocephalus, porencephaly, and microencephaly.

In the BVDV-positive brains (21 cases), cerebellar hypoplasia (13), hydranencephaly (7), microencephaly (4), hydrocephalus (2), and porencephaly (1) were noted in addition to perivascular and perineuronal oedema (9 and 7 cases, respectively), inflammatory responses such as perivascular cuffing, focal and diffuse gliosis (8 and 6 cases, respectively), and diffuse hypomyelination (7). Occasionally, there were some less remarkable lesions. Hypoplasia of the rostral and caudal colliculi, cerebellar fold hypoplasia, nucleus hypoplasia of the anterior colliculus, unilateral neuronal agenesis in nuclei of the anterior colliculus, rarefied and disorganised neurons in the nuclei seen in the obex, neuronal agenesis in the red nucleus, and multifocal hypomyelinogenesis in the thalamus were diagnosed as malformations. Ventricular ependymal proliferation was noted and designated as a proliferative process. The inflammatory changes constituted of focal mild meningitis with submeningeal oedema and non-suppurative encephalitis. Degenerative changes such as demyelination in the red nucleus and hyalinisation of the cerebral vascular walls were also encountered. Lafora bodies near the hippocampus and in the Purkinje cells, and vacuole formation in cerebral neurons were also diagnosed.

Among the 13 hypoplastic cerebella, in seven cases hypoplasia and dysgenesis were limited to Purkinje cell layer. In three cases concurrent hypoplasia of all three cellular layers (granular, Purkinje, molecular) was recorded where only choroid plexus was formed (Fig. 3). Simultaneous

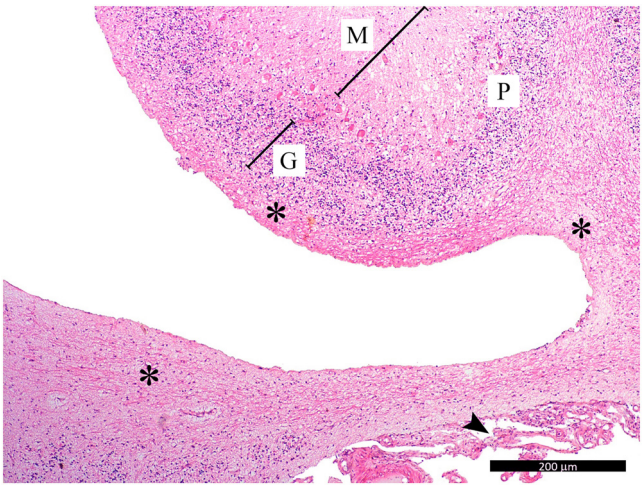

Fig. 3. Calf. Cerebellum. BVDV infection. Concurrent hypoplasia of all three cortical cellular layers. Distorted architecture is depicted with rarefied molecular (M), Purkinje (P), and granular (G) cell layers, prominent choroid plexus (arrowhead), and massive white matter (asterisks). Microphotograph, HE. Bar = 200 µm

hypoplasia of Purkinje and molecular cell layers were noted in one brain. Concurrent Purkinje and granular cell depletion were also noted in one patient (Fig. 4). No remarkable pathological lesions were observed only in one case where BVDV antigen was detected (Table 2).

In the AKAV-positive brains (6), cerebellar hypoplasia (4), hydranencephaly (3), porencephaly (2), and hydrocephalus (1) were noted in addition to inflammatory changes such as focal and diffuse gliosis (3), perivascular cuffing (2), glial nodule formation (1), and perivascular and perineuronal oedema (2 and 1 cases, respectively). Hypomyelination (1) and Purkinje cell ectopia (1) were the degenerative and dysplastic lesions encountered. Of the four hypoplastic cerebella, one case of Purkinje cell hypoplasia

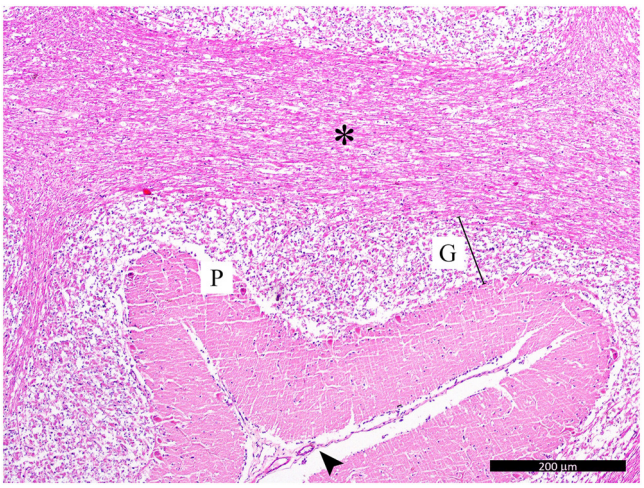

Fig. 4. Calf. Cerebellum. BVDV infection. Concurrent hypoplasia of Purkinje (P) and granular (G) cell layers is evident, along with a massive white matter (asterisk). The meningeal layer is also present (arrowhead). Microphotograph, HE. Bar = 200 µm

was detected in addition to one case of concurrent hypoplasia of granular and molecular cell layers, and two cases where all three cellular layers of the cerebellum were hypoplastic. The only case of Purkinje cell ectopia (Fig. 5) was noted in a severely hypoplastic cerebellum, where all three cellular layers were simultaneously hypoplastic (Table 2).

DISCUSSION

The results derived from this study are in complete harmony with the findings of previous studies (Montgomery, 2007; Montgomery et al., 2008) and state that the fetal brain is the primary and most important target of persistent infection with BVDV.

As Queiroz et al. (2013) and Cantile and Youssef (2016) have declared, developmental manifestations of teratogens are uniquely correlated to the nature of the agent, as well as the gestational or perinatal period during which the infection has occurred. 'Cerebellar growth patterns' and anomalies reflect such information. A variety of viral teratogens including BVDV and AKAV cause necrosis in germinative cells of the external granular layer of the cerebellum, leading to cerebellar hypoplasia. Vascular damage has also been demonstrated in BVDV infection. Agerholm et al. (2015), and Cantile and Youssef (2016) believe that cerebellar hypoplasia is the most frequent and most characteristic developmental anomaly of the brain in BVDV infection. In the present study, hypoplasia of cerebellar cellular layers and vascular lesions were observed and cerebellar hypoplasia was the most frequent malformation. Although ectopia of Purkinje cells is defined as a hallmark of cerebellar atrophic process (Cantile and Youssef, 2016), and has been related to BVDV infection (Tunca et al., 2006), in this study Purkinje cell ectopia was noted in an AKAV-positive calf. However, Purkinje cell hypoplasia (7 cases), granular cell layer hypoplasia (1 case), concurrent hypoplasia of Purkinje and molecular cell layers (1 case), concurrent hypoplasia of Purkinje and granular cell layers (1 case), and hypoplasia of all three cerebellar cellular layers (3 cases) were present in BVDV-positive calves.

BVDV can readily be detected by RT-PCR, and researchers have noted that RT-PCR is one of the most sensitive methods for BVDV detection and that it is preferred to virus isolation (Lanyon et al., 2014). Hydranencephaly, microencephaly, hydrocephalus and porencephaly have been described in previous studies as the outcomes of infection with BVD virus (Porter et al., 2010; Atmaca et al., 2012; Lanyon et al., 2014; Agerholm et al., 2015), and in the current study these anomalies were observed in fetal brains where BVDV antigen could be detected utilising RT-PCR.

Prior studies have explained that brain lesions can only be seen when the brain is infected in the first trimester of gestation, inducing persistent infection (Montgomery et al., 2008). Thus, the only BVDV-positive brain lacking histopathological lesions could be attributed to transient infection, though serological investigations are necessary for conclusive statements.

Table 2. The frequency of detected viral agents and lesions observed in each group

		Frequency																		
		Lesions																		
													Hypoplasia of cerebellar layers							
PCR results	Count	CH	HA	M	H	P	GN	Gl	PVC	HM	PNE	PVE	G	P	M	GM	PM	PG	GMP	PE
BVDV+	21	13	7	4	2	1	6	6	8	7	7	9	1	7	0	0	1	1	3	0
AKAV+	6	4	3	0	1	2	1	3	2	1	1	2	0	1	0	1	0	0	2	1
SBV+	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Negative	15	9	10	0	2	2	0	1	0	0	0	0	0	0	0	2	0	0	0	0

†CH: Cerebellar hypoplasia, HA: Hydranencephaly, M: Microencephaly, H: Hydrocephalus, P: Porencephaly, GN: Glial nodule, Gl: Focal and diffuse gliosis, PVC: Perivascular cuffing, HM: Hypomyelination, PNE: Perineuronal oedema, PVE: Perivascular oedema, G: Granular, P: Purkinje, M: Molecular, GM: Concurrent granular and molecular, PM: Concurrent Purkinje and molecular, GMP: Concurrent granular, Purkinje and molecular, PE: Purkinje cell ectopia.

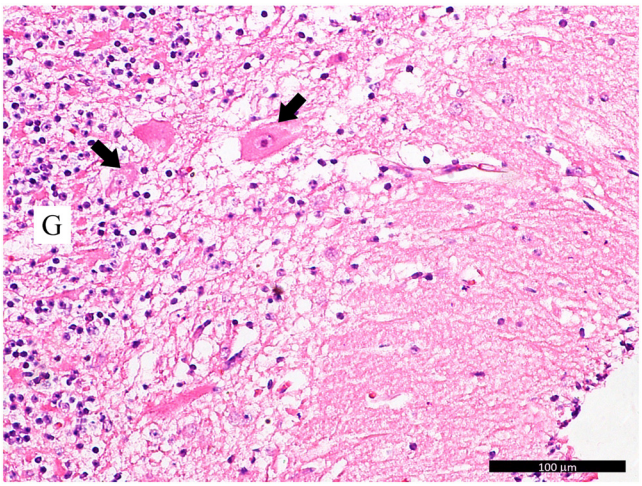

Fig. 5. Calf. Akabane virus infection. Ectopic Purkinje cells (arrows) are present within the granular cell layer (G). Microphotograph, HE. Bar = 100 µm

Non-communicating hydrocephalus secondary to viral infections has not been described (Summers et al., 1995); thus, it can be concluded that non-communicating hydrocephalus was not the mechanism involved in brains affected with hydrocephalus in which BVDV and AKAV were detected.

Hypoplasia of granular cell layer of the cerebellum is known to be associated with necrosis of external granular cell layer as an outcome of BVDV infection (Lanyon et al., 2014; Agerholm et al., 2015). In the current study, hypoplasia of the granular cell layer alone was observed in one brain. In one case, concurrent hypoplasia of Purkinje and molecular layers was seen, and three cerebella showed simultaneous hypoplasia of all three cellular layers. In one case, Purkinje and granular cell layers were hypoplastic. Given that in a previous study (Tunca et al., 2006), concurrent hypoplasia of granular and Purkinje layers, and simultaneous hypoplasia and degeneration of granular and molecular layers were seen and attributed to BVDV infection, our findings are partially in harmony with those of the above-mentioned study.

Ectopia of Purkinje cells has been correlated to BVDV infection (Agerholm et al., 2015). In the current study, only one case of Purkinje cell ectopia was noted and the calf was in the AKAV-positive group.

As in a previous study (Agerholm et al., 2015), cerebral and cerebellar porencephaly was associated with BVDV infection, in the current study the same lesion was observed in the cerebrum where BVDV antigen was detected.

All brains affected by hydranencephaly were similar to the descriptions of previous researchers (Agerholm et al., 2015) where cerebral hemispheres were replaced with fluid-filled sacs covered by thin and translucent leptomeninges.

Microencephaly has been described as a less frequent outcome of BVDV and AKAV infection (Agerholm et al., 2015; Cantile and Youssef, 2016). In this study, microencephaly constituted four cases; more frequent than hydrocephalus and porencephaly.

Porencephaly and microencephaly have also been reported in AKAV infection (Vandevelde et al., 2012; Haligur et al., 2014) and in the present study in two cases of porencephaly, AKAV was detected, but microencephaly was absent among AKAV-positive cases.

Diffuse or focal gliosis and mononuclear, especially lymphocytic, perivascular cuffs (PVC) are known as the most prominent features of viral encephalitis (Summers et al., 1995; Porter et al., 2010; Haligur et al., 2014; Cantile and Youssef, 2016). These lesions were also observed in the current study, where BVDV and AKAV antigens were detected.

Neuronal intracytoplasmic vacuole formation is stated as an outcome of Akabane infection (Haligur et al., 2014). In the present study, the same lesion was seen in three cases, two of which were BVDV positive while in the other case none of the studied pathogens were detected.

Cerebellar hypoplasia has been commonly correlated to BVDV and SBV infection (Queiroz et al., 2013; Agerholm et al., 2015), and occasionally to late AKAV infection (Vandevelde et al., 2012; Cantile and Youssef, 2016). In the present study, four cases of cerebellar hypoplasia were

AKAV positive, consisting of hypoplasia of Purkinje cell layer (one case), concurrent hypoplasia of granular and molecular cell layers (one case), and hypoplasia in all three cellular layers (two cases).

Cerebellar hypoplasia can be concurrently present in brains affected by hydranencephaly (Montgomery et al., 2008; Cantile and Youssef, 2016). This synchrony was seen in eight cases, two of which were AKAV positive, three were BVDV positive, and in three cases none of the studied viral agents, including SBV, were detected.

In conclusion, various global neurologic and histopathological presentations in calves suffering from intrauterine BVDV and AKAV infections stem from differences in the severity of lesions of involved cells. Accordingly, the diversity of lesions in different studies is expectable. Besides genetics, pathologists and clinicians must consider viral aetiology, most importantly intrauterine BVDV and AKAV, when facing developmental abnormalities of nervous tissue. In the same vein, cerebellar abnormalities must first be checked for BVDV infection, especially in Iran.

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