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Toroviruses Affecting Animals and Humans: A Review

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ABSTRACT

Toroviruses are responsible for causing gastroenteritis in animals and humans. These are enveloped viruses with non-segmented and positive-sense (single stranded) RNA genome of 20 to 25 kilobases, pleomorphic and are associated with diarrhea in cattle, sheep, goat, pig and other animals and also in human beings. Morphological appearance of viruses is spherical/oval, elongated or kidney shaped. These show Torovirus-like (tubular and torus nucleocapsid in the cytoplasm of infected cells) appearance under the electron microscope and are approximately 100-140 nm in diameter, surrounded by club-shaped projections of 15-20 nm in length. Clinical signs of the disease are pyrexia, diarrhoea, dehydration, lethargy and depression in calves as well adults. In calves, the virus may lead to anorexia, mucoid faeces and neurological signs like generalised weakness, paralysis, inability to stand along with trembling and sudden death. In faecal samples, these can be identified by electron microscopy. Immunological tests include Immuno-electron Microscopy (IEM), Haemagglutination Inhibition (HI), Enzyme Linked Immunosorbent Assay (ELISA) and southern blot. The molecular assays are reverse transcription-polymerase chain reaction (RT-PCR), nested-RT-PCR and SYBR Green real-time RT-PCR. Combined use of ELISA and RT-PCR are considered is a practical approach for epidemiological studies of bovine torovirus. At present, no vaccine is available for torovirus. The only control measures available are good hygiene and sanitary conditions along with isolation of infected animals. The present review highlights the salient features of the torovirus, their epidemiology, clinical signs, diagnosis, treatment and suitable prevention and control measures to be adopted.

Key words: *Torovirus*, animals, cattle, swine, humans, diarrhoea, epidemiology, diagnosis, prevention, control

INTRODUCTION

Toroviruses (genus *Torovirus*, family Coronaviridae) are responsible for causing gastroenteritis in animals (cattle, swine) and humans (Weiss *et al.*, 1984a, b; Beards *et al.*, 1986; Weiss and Horzinek, 1987; Studdert, 1996; Kroneman *et al.*, 1998; Jamieson *et al.*, 1998; Holmes, 2001;

Gonzalez *et al.*, 2003; Wilhelmi *et al.*, 2003; Lodha *et al.*, 2005; Sellon, 2007). In the year 1972, isolation of a virus had been done in Berne in Switzerland from a horse which did not show any reaction with antibody against viruses of equine. An unclassified virus of similar kind was isolated in the year 1982 from calves in Breda, Iowa. Subsequently, in the year 1984, particles that resembled these viruses were discovered in the faeces of human (De Groot *et al.*, 2011). As per the International Committee on Taxonomy of Viruses (ICTV) four species of torovirus are *Equine torovirus* (EToV), *Bovine torovirus* (BToV), *Porcine torovirus* (PToV) and *Human torovirus* (HToV) (www.ictvonline.org). Toroviruses can cause serious/fatal diarrhea in cattle while in swine are implicated with asymptomatic enteric infections. This virus may lead to nosocomial viral gastroenteritis (NVG) in pediatric hospital (ICTVdB Management, 2006; Gubbay *et al.*, 2012).

ETIOLOGY

Toroviruses are the members of the genus *Torovirus* of the family Coronaviridae, sub family Torovirinae, order Nidovirales (Shin *et al.*, 2010; Aita *et al.*, 2012). These include Berne Virus (BEV), Breda Virus (BRV), *Bovine torovirus* (BoTV), *Equine torovirus* (EToV), Prototype Berne Virus and *Porcine torovirus* (PToV). Toroviruses cause enteric infections and gastroenteritis in cattle, swine and humans (Weiss *et al.*, 1984a; Horzinek *et al.*, 1987; Koopmans and Horzinek, 1994; Studdert, 1996; Jamieson *et al.*, 1998; Hoet *et al.*, 2002; Gonzalez *et al.*, 2003; Wilhelmi *et al.*, 2003; Lodha *et al.*, 2005; Sellon, 2007). Toroviruses are enveloped viruses with non-segmented and positive-sense (single stranded) RNA genome of 20 to 25 kilobases in length; virions are pleomorphic (100 to 140 nm diameter) and possess large protein spikes on their surface resembling peplomers of coronaviruses (Spaan *et al.*, 2005; Lai *et al.*, 2007; Perlman and Netland, 2009). Within the genus *Torovirus* four species have been described. *Equine torovirus* (EToV), also known as Berne Virus (BEV), is the first virus to be recognized. This particular virus is also the prototype species of the genus as in cell cultures it is the only adopted virus to be grown. *Bovine torovirus* (BToV) is the next one to be discovered and the pathogenesis of this particular virus has been investigated by infecting gnotobiotic calves experimentally (Woode, 1987; Hoet and Horzinek, 2008). Several reports are available regarding the presence of *Human torovirus* (HToV) particles in faeces. *Porcine torovirus* (PToV) initially was detected in faecal samples of pig by electron microscopy (Lavazza *et al.*, 1996; Jamieson *et al.*, 1998; Hoet and Saif, 2004). EToV, BToV and PToV are related serologically. Against each of the structural protein antibodies arise during the process of natural infection. Virus neutralization antibodies are generated against the spike protein; EToV gets cross-neutralized by the sera from animals infected with BToV or PToV (King *et al.*, 2011).

In mature torovirus, the nucleocapsid is torus-shaped, hence the viruses are named as torovirus (Duckmanton *et al.*, 1997). Toroviruses are very closely related and consists of 3 species in a single genus (Zlateva *et al.*, 2011). These show Torovirus-like (tubular and torus nucleocapsid in the cytoplasm of infected cells) appearance under the electron microscope (Shin *et al.*, 2010; Aita *et al.*, 2012). In cross sections, virions show typical twin circular structures (a torus morphology of the nucleocapsid). The 5'-most two-thirds of the genome have huge overlapping open reading frames (ORF 1a and 1b) that encode polyproteins from which the various subunits of the viral replicase/transcriptase are originated. There are four cistrons of 5 kb, 0.7, 1.2 and 0.5 kb downstream of ORF 1b, as ordered from 5' to 3', which encode the structural proteins-spike (S), Membrane (M), Hemagglutinin-esterase (HE) and Nucleocapsid (N) proteins, respectively (Draker *et al.*, 2006; Aita *et al.*, 2012; Cong *et al.*, 2013). It is important to note that the HE is

associated with enteritis (Langereis *et al.*, 2009; Pignatelli *et al.*, 2013). The four structural proteins are translated from a 3'-coterminally nested set of subgenomic mRNAs, produced by discontinuous and non-discontinuous RNA synthesis (Snijder *et al.*, 1990; Snijder and Horzinek, 1993; Van Vliet *et al.*, 2002).

Antigenic cross-reactivity between human and animal toroviruses has been evidenced by hemagglutination inhibition and immunoelectron microscopy (Beards *et al.*, 1986; Duckmanton *et al.*, 1999; Horzinek, 1999; De Groot, 2007). Toroviruses have not been propagated in cell cultures, except the Swiss equine isolate Berne virus (BEV), which could be propagated in embryonic mule skin cells and is the only cell culture-adapted torovirus (Weiss *et al.*, 1983). Two contiguous sequences have been obtained by sequence analysis of the complementary deoxyribonucleic acid (cDNA) derived from the genomic ribonucleic acid (RNA) of Torovirus. The first one is of 1580 nucleotides representing the 5' end of the genome which comprises a large non-translated region at the 5' end along with a downstream sequence that encodes the N-terminal amino acids of the replicase. On the basis of the assumption that replicase gene of torovirus consists of only two ORFs the ribosomal frame shift site is connected by one of the genome region continuing down to the 3' poly adenylated (A) tail. Such description of the toroviral genome is significant in understanding the replication strategy of the virus (Brierley *et al.*, 1990; Chen *et al.*, 1993). Propagation of Bovine toroviruses had not been reported in bovine organ or cell culture or embryonated eggs; the only way for its propagation include inoculation of susceptible (gnotobiotic or colostrum-deprived) calves. Although cell culture-adapted BEV has not been demonstrated to be pathogenic experimentally, neutralizing antibodies have been observed in most adult horses (Ito *et al.*, 2010).

From children suffering from gastroenteritis, fringed particles (pleomorphic) that resembles particles designated previously as toroviruses have been observed in substantial number. They have been shown as toroviruses on the basis of high level of concordance between torovirus-like particle identification by the use of electron microscopy and a positive enzyme immunoassay with antiserum of Breda virus. On the basis of morphology as well as immunospecific interactions with antiserum of Breda virus further confirmation of the presence of Toroviruses in human stool specimen has been done. These human viruses have shown high degree of homology of the genomic 3' end with that of the Berne and Breda viruses. Such data supports the fact that these toroviruses are infectious in nature (Ford-Jones *et al.*, 1990; Koopmans *et al.*, 1993; Duckmanton *et al.*, 1997; Jamieson *et al.*, 1998).

EPIDEMIOLOGY

The type species of the genus *Torovirus* is the Berne virus (BEV), an equine torovirus originally isolated in 1972 from rectal swab of a horse with hepatic and gastrointestinal/diarrheic disease in Berne, Switzerland (Weiss *et al.*, 1983). However, an etiological link between Berne virus and equine disease has not been established. Bovine torovirus (earlier known as Breda virus) was for the first time isolated from stools of neonatal diarrheic calves in Breda, Iowa, in 1982 during an outbreak of neonatal calf diarrhea, in which 15% of the affected animals died (Woode *et al.*, 1982). Since then, toroviruses have been detected and confirmed in ungulates (goats, sheep), horses, pigs, lagomorphs, rodents, domestic cats and other potential hosts including human beings especially in children in several countries (Beards *et al.*, 1986; Woode, 1994; Duckmanton *et al.*, 1997, 1998; Kroneman *et al.*, 1998; Ali and Reynolds, 2000; Cavanagh, 2005; Koopmans *et al.*, 1993, 1997; Ito *et al.*, 2010; Alonso-Padilla *et al.*, 2012).

Details of the antigenic relationship between toroviruses and the epidemiological features of bovine torovirus infection remain unknown. A cytopathogenic Bovine torovirus (designated the Aichi/2004 strain) was isolated in a human rectal adenocarcinoma cell line (HRT-18) from the ileum contents of a calf with diarrhea. Studies also indicated that the Bovine torovirus infection might be common in cattle in Japan (Kuwabara *et al.*, 2007). Previous studies found that bovine toroviruses were prevalent in calf diarrheal cases in USA (36.4%) and Japan (18%), while less frequent in Korea (2.9%) and Austria (5.2%) (Duckmanton *et al.*, 1998; Haschek *et al.*, 2006; Kirisawa *et al.*, 2007; Park *et al.*, 2008).

Limited seroepidemiologic studies indicate that the virus is present in Europe and the United States. In the Netherlands, prospective studies have been conducted wherein examination of viruses have been done in symptomatic as well as asymptomatic calves by means of ELISA. This has demonstrated the presence of torovirus in 6.4% of calves having diarrhea in comparison to 1.7% of asymptomatic controls. The presence of BoTV in wide spread manner in the Netherlands and Germany, Switzerland, the United Kingdom as well as the United States have been revealed by epidemiological studies. The role of BoTV in respiratory as well as digestive and reproductive disorders of cattle has been revealed by a study conducted in Belgium (Moerman *et al.*, 1986; Van Kruiningen *et al.*, 1992; Meng, 2012).

In Canada and South Africa, along with countries in Europe like Italy, Hungary and most recently in Spain, porcine torovirus has been reported; however in China, PToV has not been reported (Penrith and Gerdes, 1992). Enzyme linked immunosorbent assay (ELISA) along with real time reverse transcriptase-polymerase chain reaction (RT-PCR) assay have been developed in order to detect as well as to quantitate PToV in clinical specimens, the results of which have indicated the high prevalence of PToV in porcine livestock of Spain. Longitudinal study has been conducted later on to analyze the samples collected from animals at various time points during the life of the piglet. Such study has revealed that infection in animals occur soon after weaning when there is decline in the maternal protection which is transferred through the colostrums (www.cnb.csic.es).

Brown *et al.* (1988) reported that in Southern India the prevalence of neutralizing antibody to Berne virus was high in sera obtained from cattle (49%), horses (38%) and sheep (36%). Widespread evidence of exposure to Berne virus is indicated by the presence of neutralizing antibody in the sera of cattle, goats, sheep, pigs, rabbits, cats and wild mice. No evidence however indicates that this virus is associated with clinical disease in horses or any other species (Weiss *et al.*, 1984a, b). Experimental inoculation of the virus into two foals induced neutralizing antibody but did not produce any clinical signs.

Despite their potential veterinary/clinical significance, much is to be recognized about epidemiology/prevalence and molecular genetics of toroviruses. Phylogenetic and evolutionary relationships among torovirus field variants evidences for multiple intertypic recombination events (Smits *et al.*, 2003; Shin *et al.*, 2010). Replicase polyproteins are processed primarily by the chymotrypsin-like main proteinases (M^{pro}s). Comparative sequence analysis of polyprotein 1a of *Equine torovirus* (EToV) strain Berne revealed a serine proteinase domain, flanked by hydrophobic regions (Smits *et al.*, 2006). The torovirus M^{pro} uses serine instead of cysteine as its principal nucleophile. The transition from serine- to cysteine-based proteolytic catalysis (or vice versa) must have happened more than once in the course of nidovirus evolution; so it is of interest that a mutant ETV M^{pro} with a Ser¹⁶⁵-Cys substitution retained partial enzymatic activity.

CLINICAL SIGNS

Toroviruses cause diarrhea in calves by infecting villous and crypt enterocytes of the mid-jejunum, ileum, colon and cecum and inducing villous atrophy and necrosis of the crypts (Koopmans *et al.*, 1991a; Koopmans and Horzinek, 1994; Hoet *et al.*, 2003a). Clinical signs are pyrexia, diarrhoea, dehydration, lethargy and depression in calves as well adults. In calves, it may lead to anorexia, mucoid faeces and neurological signs like generalised weakness, paralysis, inability to stand along with trembling and sudden death. The diarrhea in calves is of mild to moderate form in experimental as well as field conditions. In case of 5-6 months age group of cattle, in both dairy and beef herd, *Bovine torovirus* (BoTV) has been detected. When BoTV is inoculated either orally or intranasally both the small as well as large intestines get affected that result in moderate to watery diarrhea by 24-72 hours post-inoculation. This is associated with depression as well as anorexia lasting for 3-5 days. The cytopathic effects along with necrosis occur due to virus infection of the epithelial cells from the middle as well as lower parts of the villi that extends into the crypts cells (Snijder *et al.*, 1994; Snijder and Spaan, 1995; Radostits *et al.*, 2000). Respiratory problems viz., laryngitis, tracheitis and pneumonia have also been documented with these viruses (Duckmanton *et al.*, 1999). In cats, the disease is associated with diarrhea and protrusion of nictitating membranes, while pigs show no clinical signs but can shed the torovirus.

DIAGNOSIS

For diagnosis, detection of torovirus antigen in faeces or rectal swabs is considered significant. In fecal samples, coronavirus-like particles (spherical, oval, elongated, or kidney-shaped; 100-140 nm with club-shaped projections of 15-20 nm) can be identified by electron microscopy (negative staining) (Aita *et al.*, 2012). Immunological tests include Immuno-electron Microscopy (IEM), Haemagglutination Inhibition (HI), Enzyme Linked Immunosorbent Assay (ELISA) and Southern blot. In Spanish swine herds, a large sero-epidemiological survey has been conducted particularly for *Porcine torovirus* (PToV) on the basis of availability of a cost-effective as well as feasible ELISA. For anti-PToV antibodies, this ELISA methodology had been shown to be sensitive as well as specific. This assay also shows a high degree of correlation with the heterologous neutralization assay concerning EToV. On the basis of ELISA it has been revealed that the antibody level against PToV varies greatly in young animals with their age (Kroneman *et al.*, 1998; <http://epp.eurostat.ec.europa.eu>). ELISA and HI assay have been used combinedly for detection of BoTV, which is suitable to detect the faecal shedding of BoTV. Such combination of serological assays is helpful for differentiation of BoTV shedding calves as well as non-shedders in relation to disease as well as treatment. Especially for detection of the virus in feed lot cattle such combined efforts have been taken (Hoet *et al.*, 2002).

The molecular diagnostic assays for Torovirus infection are reverse transcription-polymerase chain reaction (RT-PCR) using torovirus-specific primers, one step multiplex reverse transcription-PCR, nested-RT-PCR targeting the Nucleocapsid (N) gene and SYBR Green real-time RT-PCR (Brown *et al.*, 1987; Koopmans *et al.*, 1991b; Hoet *et al.*, 2002, 2003a; Matiz *et al.*, 2002; Pignatelli *et al.*, 2010a; Hosmillo *et al.*, 2010; Fukuda *et al.*, 2012; Alonso-Padilla *et al.*, 2012; Cho *et al.*, 2013; Nogueira *et al.*, 2013). Use of SYBR green as fluorescent dye in real time PCR reduces the time taken in the test and risk of contamination of samples. All these advantages have made the real time assay more suitable for the diagnosis of viruses particularly in epidemiological

studies involving the analysis of large number of sample size (Oka *et al.*, 2006; Kim *et al.*, 2007; Meleg *et al.*, 2008; Prickett *et al.*, 2008; Pignatelli *et al.*, 2010b). Differentiation of torovirus from other coronaviruses can be done using Immuno-electron Microscopy (IEM). Propagation of torovirus in cell culture is difficult except for equine torovirus. Among bovine torovirus, only Aichi/2004 strain has been isolated human rectal adenocarcinoma cell line (HRT-18) (Boom *et al.*, 1990; Kuwabara *et al.*, 2007; Ito *et al.*, 2010). Combined use of ELISA and RT-PCR are considered as practical approach for epidemiological studies of bovine torovirus (Hoet *et al.*, 2003b). Sequencing and phylogenetic analysis may also be used to establish the phylogenetic relationship between different strains of viruses (Nogueira *et al.*, 2013; Sun *et al.*, 2013).

TREATMENT

There is no specific treatment. However, animals suffering from torovirus infection can be treated symptomatically by fluid therapy to prevent dehydration. Antibiotics may be used to check the secondary bacterial infections.

PREVENTION AND CONTROL

At present no vaccine is available for torovirus. This is because of the variable role of toroviruses as pathogens. For prophylaxis, however colostrum containing antibodies against BTovV can be used (Maclachlan and Dubovi, 2010). The affected animals must be isolated from apparently healthy animals. Proper personal hygiene like wearing of gloves, boots and gowns are necessary in the farms during the handling of affected animals to avoid chances of cross contamination. Faecal matter and bedding material should not be spread on pastures otherwise these materials may contain viruses that can spread infection to other animals too. These materials may be destroyed by composting, which is found effective in killing of infectious agents. Floor and walls of animal shed should be properly disinfected using suitable detergents and disinfectants. For emerging infection such as torovirus infection there is need to strengthen public health and animal surveillance systems. These surveillances will definitely help in reducing the emergence of such an important pathogen and its further transmission and spread to another susceptible host. Apart from these practices, suitable prevention and control measures like good management practices including of hygiene and sanitary conditions along with strict biosecurity measures need to be maintained to combat toroviruses in bovine, equine, porcine and human beings.

Keeping in view the One Health concept, quick and accurate diagnostic tests supported with appropriate surveillance systems need to be exploited fully for detection of toroviruses affecting both animals and humans (Hoet *et al.*, 2003b; Schmitt and Henderson, 2005; Belak, 2007; Kim *et al.*, 2007; Kirisawa *et al.*, 2007; Hosmillo *et al.*, 2010; Ito *et al.*, 2010; Pignatelli *et al.*, 2010b; Shin *et al.*, 2010; Deb and Chakraborty, 2012; Fukuda *et al.*, 2012; Deb *et al.*, 2013; Dhama *et al.*, 2012, 2013a, b, 2014). Recent advances in vaccines and therapeutic modalities also need to be exploited to counter toroviruses and their associated public health concerns (Meeusen *et al.*, 2007; Dhama *et al.*, 2008, 2013c-f; Mahima *et al.*, 2012; Tiwari *et al.*, 2014).

CONCLUSION AND FUTURE PERSPECTIVES

The present review is an attempt to alert the human and veterinary health researchers about the existence and clinical disease due to torovirus in animals as well as man especially children. There is requirement of continuous vigilance for potential zoonotic viruses including torovirus. For

this purpose, detailed survey involving large population size, longitudinal cohort study or animal challenge study is warranted for determining the clinical significance of torovirus infection. Toroviruses need much to be studied and understood. Because of somewhat close phylogenetic relationship to coronaviruses these viruses may in many respects represent “missing links” in comparative nidovirus studies. The ungulate toroviruses apparently display host species preference. Toroviruses may be even more promiscuous than the coronaviruses and arteriviruses, the closest relatives. Research should also be made to investigate the interactions of toroviruses with different tissues, their persistence and immune responses of host to these infections. Modern diagnostics tools and techniques are being exploited for detecting torovirus infections in animals and humans. Toroviruses need much to be studied and understood, for which purpose research need to be strengthened for carrying out extensive epidemiological surveys, studying viral pathogenicity, developing rapid diagnostics and a suitable vaccine for safeguarding health of animals and humans from these viruses.

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