

Mini Review



Picobirnavirus: A Putative Emerging Threat to Humans and Animals

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Abstract | Diarrheal diseases remain fatal threat to human and animal population with the emergence of new types of pathogens. Among them, viral gastroenteritis plays a lion share with a number ranging over 100 different types including emerging and re-emerging types of viruses. Recent viral metagenomics studies confirm the co-existence of viruses in gastrointestinal tract of several different host species. A Picobirnavirus, consisting of 2 segments, has recently attained attention due to its wide host range and genetic variability. Until 2011, these small viruses were not considered as a separate virus family, when a new family (Picobirnaviridae) was approved by the International Committee on Taxonomy of Viruses (ICTV). Currently two distinct genogroups (GG-I and GG-II) and one predicted genogroup (GG-III) are included in the *Picobirnaviridae* family. Recently, picobirnavirus infections have been reported from almost all species including wild animals where persistent infection of the virus is also reported. Picobirnaviruses (PBVs) are also reported as opportunistic pathogens in immuno compromised hosts including HIV infected patients. Presence of atypical picobirnaviruses with shorter genomic segments along with genetic closeness of animal and human PBVs and its ability to infect immuno-compromised hosts pose a heavy threat for all human and animal. Currently RNA dependent RNA polymerase based RT-PCR detection is considered as a rapid and sensitive method for detection of PBV. SYBR based real time PCR, RNA PAGE analysis, electron microscopy also serve as detection methods for PBVs. Unavailability of permissive cell lines or animal models remain hurdles for studying the different molecular mechanisms for viral entry, disease causation or even the mode of persistence in reservoir hosts.

Keywords | Picobirnavirus, Enteritis, Genogroups, Diagnosis, Epidemiology

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astrointestinal tract infections are now recognized as crucial health problem and are one of the major challenges to growing livestock sector as well as human population throughout the world (Kosek et al., 2003; Clark and McKendrick, 2004). Amid several causes, enteric viruses inflict greater risk and currently include over 100 viruses, few of which include emerging, re-emerging and novel pathogens, that affect animals and/or humans at various stages of life (Wilhelmi et al., 2003; Oude-Munnink and van dek Hoek, 2016). The faecal virome analysis has been able to reveal several viruses associated with acute gastroenteritis, such as novel enteric coronaviruses, bocavirus, kobuvirus, sapelovirus, salivirus, cosavirus, and others. Along with the other recently recognized virus-

es, Picobirnavirus (PBV) is highly versatile because of its broad host range and genetic diversity. PBV is inflicting potential jeopardy for a number of host species including humans. PBV has been detected in several animal and environmental samples through various molecular techniques (Ganesh et al., 2014). It is an ultra-small (35 nm in diameter), non-enveloped virus possessing two genomic segments of double-stranded RNA. In its initial period of detection (1988), it was named a 'Birna-like' virus under the family *Birnaviridae* (Pereira et al., 1988a; Pereira et al., 1988b). Upon availability of further sequence details during the next one decade (1990-2000), it was classified as a new family member with approval of International Committee on Taxonomy of Viruses (ICTV) (Delmas, 2011).



It exhibits two types of genome profiles (large and small) on RNA-PAGE following silver impregnation, which is based on migration distance and size of its 2 genomic segments. The large genomic profile is characterized by segments with size of 2.7 kbp and 1.9 kbp as compared to the smaller one where segments correspond to 2.2 kbp and 1.2 kbp, respectively (Malik et al., 2014). The capsid protein and the viral RNA-dependent RNA polymerase (RdRp) of PBV is encoded by genomic segment 1 (2.2–2.7 kbp) and 2 (1.2-1.9 kbp), respectively. On the basis of RdRp gene sequence diversity, PBVs are classified into two genogroups, namely genogroup-I and II (Rosen et al., 2000). Besides, a third genogroup has also been reported in humans more recently in 2014 (Smits et al., 2014). Genogrouping based on RdRp gene helps in the identification of specific viral genogroups circulating in animals across the different countries. Despite its evolutionary association with "partitiviruses" especially fungi partitiviruses, the PBV is classified under a new family 'Picobirnaviridae' with a single genus, Picobirnavirus. It includes two species namely human Picobirnavirus (type species) and rabbit Picobirnavirus (designated species) (Delmas, 2011).

Since its discovery in 1988, PBV has been detected in faecal specimens of numerous domestic and captive animal species such as rats (Pereira et al., 1988b; Fregolente et al., 2009), chickens (Alfieri et al., 1989; Leite et al., 1990; Monteiro et al., 1991; Tamehiro et al., 2003; Fregolente et al., 2009; Ribeiro et al., 2014), hamsters (Pereira et al., 1988b), guinea pigs (Pereira et al., 1989), pigs (Gatti et al., 1989; Chasey et al., 1990; Ludert et al., 1991; Pongsuwanna et al., 1996; Carruyo et al., 2008; Banyai et al., 2008; Martinez et al., 2010; Smits et al., 2011; Ganesh et al., 2012), dogs (Fregolente et al., 2009; Costa et al., 2004), giant anteaters (Haga et al., 1999), equine (Ganesh et al., 2011), foals (Browning et al., 1991), bovine calves (Buzinaro et al., 2003; Ghosh et al., 2009; Malik et al., 2011; Malik et al., 2014; Takiuchi et al., 2016), water buffalo calf (Malik et al., 2013), camels (Woo et al., 2014), snake (Fregolente et al., 2009), and several cat family members. It is noteworthy that PBV is not yet established as an etiological agent of diarrhea in animals (Malik et al., 2014). Although it may not be the primary cause of gastroenteritis and is most often isolated as co-infecting agent with other pathogens known to cause diarrhea such as Rotavirus (Alfieri et al., 1994; Bhattacharya et al., 2006; Bhattacharya et al., 2007; Giordano et al., 2008), Astrovirus (Bhattacharya et al., 2006; Bhattacharya et al., 2007), Caliciviruses (Banyai et al., 2003), Escherichia coli (Barreto et al., 2006), and Salmonella (Bhattacharya et al., 2007) but may have synergistic effect in association with the primary enteric causative agents. Studies on PBV detection conclude that captive animals might be serving as alternative hosts or reservoir, while domestic animals get opportunistic infection of PBVs depending upon different physiological conditions

(age, lactation, pregnancy, and stress). Moreover, the PBV infection in asymptomatic carriers is found to be persistent. The virus infects hosts in their early stages (mostly first week) of life followed by establishment of persistent infection in undefined location until the beginning of adulthood as evidenced in an adult orangutan and greater rheas (Masachessi et al., 2015). It is assumed that modulation of the viral and cellular gene expression and/or alteration in the host immune response probably play an important role in the persistence of PBVs. However, our understanding regarding the molecular mechanisms that govern the persistence/asymptomatic coexistence of PBV in captive hosts and the potential host suitability to maintain this relationship is still in its infancy. Unfortunately, the unavailability of recognized permissive cell lines and animal model for PBVs obstructs its isolation and clinico-pathological studies. Further, some unusual PBVs with smaller genome (1.7 and 1.3 kb) have also been detected in the oocysts of Cryptosporidium parvum from human and calves (Ng et al., 2014). Contrary to the typical PBVs, these unusual PBVs exhibit striking differences in coding specificity of genomic segment; as the segment 1 and 2 encodes for RdRp and capsid genes, respectively.

Picobirnaviruses are detected using Electron microscopy or molecular techniques like RNA-PAGE (polyacrylamide gel electrophoresis), reverse-transcription - polymerase chain reaction assay (RT-PCR) etc. During the early stages of life, the virus is detectable by RT-PCR only but at later stages; it is also detectable by RNA-PAGE. Epidemiological studies across the world in different animal species deploying various diagnostic techniques indicate presence of PBVs up to 65 % in porcine (Bányai et al., 2008), 3.7 % in bovines (Malik et al., 2011), 14.3 % in equines (Ganesh et al., 2011), 1.8 % in canines (Costa et al., 2004), 49.4 % in chickens (Ribeiro et al., 2014), and 47 % in other animals (Fregolente et al., 2009). The virus is also detected in sewage and surface water with a high frequency potentiating its putative zoonotic potential with emerging and/ or re-emerging threat to a number of animals in different geographical locations. Besides the gastrointestinal tract, PBV has also been isolated from the respiratory tract of pigs with no evidence of visible respiratory or other diseases (Smits et al., 2011). Likewise, it has also been identified in immunocompromised patients such as those infected with HIV (Giordano et al. 1998; González et al., 1998). A recent viral metagenomics study from Bangladesh in wild macaques reported around 184 different viruses of animal and human origin, in which 120 (65.21%) were picobirnaviruses (Anthony et. al., 2015). These reports advocate its opportunistic infection together with inhabitant setting and expand our perceptive on the tropism as well as host range of the virus. As of now, we don't have thorough understanding about the replication strategies adopted by the virus and role of adaptive immunity. Nevertheless, the evolutionary closeness of animal PBVs with human ones and detection of the virus from the sewage depict the potential threat vis-à-vis infection acquirement and cross species transmission.

We have been working on PBV since 2008 with successful development of RdRp gene based novel genus specific RT-PCR (Malik et al., 2013) and SYBR Green real-time qPCR assay (Haq et al., 2015). Molecular epidemiological studies carried on several animal host species indicate their relationship with diarrhea as alone or in combination with other enteric pathogens. We have been the first to demonstrate occurrence of PBV genogroup II in bovine species (Malik et al., 2014) and detection of PBV in bubaline species (Malik et al., 2013). Although due exploration of various hidden aspects is needed to better understand this virus and its etiopathology, which would help to devise appropriate control strategies.

CONCLUSIONS

Picobirnaviruses (PBVs) are small bi-segmented dsRNA viruses of 35 nm diameter, which are considered as one among the important gastrointestinal infection causing viruses. In 2011, ICTV classified PBVs into a new family Picobirnaviridae, which were earlier included in Birnaviridae because of its bi-segmented double stranded RNA genome. After its discovery in 1988, it has been documented from different host species including domesticated, wild animals, reptiles, birds and humans. Even though PBVs are not established as a primary etiological agent for diarrhea, their co-existence in enteritis conditions have been reported by several researchers. Till now, two established genogroups (I and II) and one putative genogroups (III) have been identified in picobirnaviruses. Absence of permissive cell lines and specific animal models hinder molecular mechanism studies for PBVs. Recent metagenomic analyses indicate enormous presence of PBV in different host species samples and environmental samples. Persistence of PBV infection as studied in wild animals and its ability to infect immuno-compromised hosts makes PBV to be noted as serious emerging infectious agents. Even though EM, RNA-PAGE, qPCR has been devised for PBV detection, RdRp based RT-PCR is considered as the rapid and sensitive diagnostic method for PBVs.

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CONFLICT OF INTERESTS

There is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors contributed equally.

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