***Review Article***

**Fowl adenovirus infection in chicken: A comprehensive review**

Abstract : The aim of the study is to provide an in-depth understanding of Fowl adenovirus infection in chicken. The Fowl adenoviruses (FAdVs) are ubiquitous in nature and found worldwide and is often isolated from asymptomatic chickens. FAdVs are known to cause many important diseases in poultry like Inclusion body hepatitis (IBH), Hydropericardium syndrome (HPS), Hepatitis hydropericardium syndrome (HHS), Gizzard erosions (GE), Proventriculitis (PV), Tenosynovitis and respiratory infections. Fowl adenovirus infection in chicken can be diagnosed based specific clinical signs, gross and histopathological lesions especially demonstration of intranuclear inclusion bodies. Electron microscopic demonstration of multiple aggregates of hexagonal adenoviral particles with basophilic intranuclear inclusions is successfully carried out for the detection FAdV. Fowl adenoviruses are non enveloped in nature, highly resistance to inactivation by heat as well as other common disinfectant. The incidence of FAdVs infections can be reduced by maintaining good management and husbandry practices. In breeder farms, strengthening of biosecurity measures and timely vaccination with updated serotypes are very important to control and prevent the infection.

**Key words:** Fowl adenovirus,Taxonomy, Epidemiology, Inclusion body hepatitis, Hydropericadial syndrome, Gizzard erosion

**INTRODUCTION**

Fowl adenoviruses are classified under the family *Adenoviridae,* genus Aviadenovirus and it includes eight species, five of which are the FAdV species consisting of *Fowl aviadenovirus A* (FAdV 1); *Fowl aviadenovirus B* (FAdV 5); *Fowl aviadenovirus C* (FAdV 4 &10) *Fowl aviadenovirus D* (FAdV 2, 3, 9 & 11) and *Fowl aviadenovirus E* (FAdV 6, 7, 8a & 8b) (Harrach *et al.*, 2012).Fowl adenoviruses (FAdVs) are common infectious agents of birds and involved in causing number of disease conditions like Inclusion body hepatitis (IBH), Hydropericardium syndrome (HPS), Hepatitis hydropericardium syndrome (HHS), Gizzard erosions (GE), Proventriculitis (PV), Tenosynovitis and Respiratory infections in poultry (McFerran and Smyth, 2000). Inclusion body hepatitis (IBH) was first described in 1963 in the USA (Helmboldt and Frazier, 1963). In 1988, a new broiler disease such as Angara disease/ Hydropericardium syndrome (HPS) was reported, the clinical signs and the course of the disease were similar to IBH (Kim *et al*., 2008; Hafez, 2011). Gizzard erosions in broiler chickens as a result of FAdV serotype 1 and 8 infections have been reported (Ono *et al*., 2001; Ono *et al*., 2003). The FAdV infection mostly affects the chickens at the age of 3-6 weeks as early as one day old chicks (Kumar *et al*.,1997; Chitradevi *et al*., 2021). Fowl adenovirus can be transmitted horizontally and vertically (Adair and Fitzgerald, 2008; Grgic *et al.*, 2006).Of late, FAdV acted as primary pathogen causing IBH without any prior immunosuppression and some strains of FAdV impair the function of the humoral and cellular immune systems themselves, thereby leading to immunosuppression and possibly paving the way for other infections (Schonewille *et al*., 2008; Chitradevi *et al*., 2021).Molecular methods such as Polymerase chain reaction (PCR) and sequencing, restriction fragment length polymorphism analysis (RFLP), real time PCR and subsequent high resolution melting (HRM) curve analysis of hexon gene was carried out for identification and serotyping of fowl adenovirus (Gaba *et al*., 2010; Mittal *et al*., 2014; Marek *et al*., 2010; Gunes *et al*., 2012).

**TAXONOMY AND STRUCTURE OF FOWL ADENOVIRUS**

Fowl adenoviruses belongs to the family *Adenoviridae* that is divided into six genera: *Aviadenovirus* infect birds, *Barthadenovirus* cause infection in squamate reptiles, birds, ruminants, marsupials and tortoises, *Ichtadenovirus* which infects fishes*, Mastadenovirus infects mammals, Siadenovirus* cause disease in birds, frog and tortoise and *Testadenovirus* infects turtles (Benko *et al.*, 2022). The fowl adenovirus serotypes can be grouped into five species on the basis of phylogeny, genome organization and the lack of significant cross-neutralization (Marek et al., 2016; Kajan et al., 2019).Under aviadenovirus genus, fowl adenoviruses are grouped into five species such as Aviadenovirus gallinae (earlier Fowl aviadenovirus D (fowl AdV-2, -3, -9, -11), Aviadenovirus hepatitidis (earlier Fowl aviadenovirus E): (fowl AdV-6, -7, -8a, -8b).Aviadenovirus hydropericardii (earlier Fowl aviadenovirus C): (fowl AdV-4,-10). Aviadenovirus quintum (earlier Fowl aviadenovirus B): (fowl AdV-5).Aviadenovirus ventriculi (earlier Fowl aviadenovirus A): ( fowl AdV-1) (Benko *et al*., 2022).

Adenoviruses are non enveloped double stranded DNA (dsDNA) viruses with an icosahedral capsid, 70-90 nm in diameter (Horne *et al*., 1959). They have characteristic fibers projecting from the penton base at each of the 12 vertices that are involved in viral attachment (Devaux *et al.*, 1987). The capsid is composed of 252 capsomeres, 240 of which are hexons and 12 of which of pentons (Ginsberg *et al.*, 1966). Hexon is the major protein of the adenovirus capsid known to have a region related to virus neutralization, serotype specificity, group and subgroup specific antigenic determinants (Toogood *et al*.,1992; Russell,2009). Fowl aviadenoviruses contain two fibers per vertex, with considerably different lengths in the case of fowl adenovirus 1 (FAdV-1) (Gelderblom and Maichle-Lauppe, 1982). In fowl adenoviruses two different fibers are present in FAdV-1, FAdV-4, FAdV-10. One fiber gene is present in other aviadenoviruses such as (FAdV - 2, FAdV - 3, FAdV - 5, FAdV -6 FAdV -7, FAdV -8a, FAdV - 8b, FAdV -9, FAdV -11. Guardado-Calvo et al., (2007) and El Bakkouri et al., (2008) established 3D structures of the FAdV-1 long and short fibers. Approximately 40 polypeptides are encoded by adenoviruses, a subset of which is included in the infectious virion: proteins II (hexon), III (penton), IIIa, IV (fiber), V (minor core, only in mastadenoviruses), VI, VII (major core), VIII, IX (only in mastadenoviruses), X, and TP (terminal protein) (Berk, 2013).

**INCIDENCE OF FOWL AVIADENOVIRUS**

Currently various serotypes of fowl aviadenovirus infection in chicken was reported worldwide. FAdVs associated with IBH outbreaks were genetically related to FAdV 2 (99.4%), FAdV 8a (99.4% to 100%) and FAdV11 (99.4% to 100%)(Ojkic *et al*.,2008; Lim *et al*.,2011). Grafl *et al*. (2012) documented an outbreak of adenoviral gizzard erosion in commercial broiler birds in Germany. Pereira *et al*. (2014) investigated the occurrence of *Aviadenovirus* in layer chickens from the poultry industry of Minas Gerais state, Brazil. Inclusion body hepatits outbreaks associated with fowl adenovirus were reported in Iran and Malaysia (Rahimi and Haghigh., 2015; Norina *et al*., 2016). In India, many researchers documented fowl adenovirus outbreaks as hydropericadial syndrome, inclusion body hepatitis and hydropericadial and hepatitis in meat type birds and gizzard erosion layer chicken with involvement of various serotypes of fowl aviadenovirus (Jadhao *et al*., 2003; Kumar *et al*., 2013; Thakor *et al*., 2012; Mittal *et al*.,2014; Trivedi *et al*.,2018; Chitradevi *et al*., 2020 and 2021). Recently FAdV serotype11associated inclusion body hepatitis reported in China and Brazil (Wang *et al*., 2023; Qiao *et al*., 2024; Batista *et al*.,2024).

**EPIDEMIOLOGY OF FOWL ADENOVIRUS INFECTION**

The Fowl adenoviruses are ubiquitous in nature and found worldwide and is often isolated from asymptomatic chickens. Inclusion body hepatitis outbreaks occurred among broiler chicks of 2 to 7 weeks of age and largest number of outbreaks occurred in 3 to 5 weeks of age (Singh *et al*., 1996; Kumar *et al*., 1997; Asthana *et al*., 2013). Inclusion body hepatitis was recorded in four days old breeder chicks in which the day old chicks have been kept in the farm without proper cleaning where the previous flock suffered from HPS and / or IBH (Pilkington *et al*., 1997). Natural cases of IBH in broilers birds with age group of 2 to 4 weeks (Thakor *et al*., 2012) and the highest number of IBH– HPS outbreaks in broiler birds of 21 to 30 days of age followed by 31 to 40 days, 1 to 10 days and youngest birds affected with this syndrome were four days of age (Mittal *et al.*, 2014; Trivedi *et al*.,2018). In India adenoviral IBH reported in one day old chicks in four commercial broiler flocks and the maximum incidences of 55 per cent (22/40) and mortality of 20 per cent were recorded between the age group of 30 and 40 days (Chitradevi *et al*., 2021). The disease incidences were high during winter season in India might be due to cold stress, huddling and possibilities for the presence of aflatoxin in the feed may aggravated the FAdV disease condition (Singh *et al*.,1996; Trivedi *et al*.,2018; Chitradevi *et al*., 2021).The incidence of IBH was more in October to November (Singh *et al*. (1996). The onset of disease occurred in hot and humid weather (Shah *et al*., 2011; Shahzad *et al*.*,* 2016) and occurrence reported throughout the year with more prevalence in winter and rainy seasons followed by summer season (Shukla *et al*., 1997; Mittal *et al.,* 2014).

Adenoviruses are reported to be highly contagious, which can spread quickly from one flock to another by vertical and horizontal means. Vertical transmission was reported as an important feature of FAdV to spread from parent birds to progenies (McFerran and Adair, 1977). There was evidence that adenovirus infections can become latent and periods of stress, such as the onset of egg production, will reactivate viral shedding (Girshick *et al*., 1980) and undetected for at least one generation in a specific pathogen free flock (Fadly *et al.,* 1980). Infected breeder sheds the virus to their progeny for three to six weeks until the immunity developed (Toro *et al*., 2001; Mazaheri *et al*., 2003). Horizontal transmission of the virus from bird to bird occurs in a flock via oro faecal route followed by further mechanical spread of the disease with faecal contamination (McFerran and Adair, 2003; Balamurugan and Kataria, 2004).The virus can also be spread through fomites, personnel and vehicles. The incubation period of the virus following natural infection ranges from 24 to 48 hours (Adair and Fitzgerald, 2008). There was no evidence of vertical transmission in birds with a strong immune response (Philippe *et al*., 2007). Adenoviruses are often reactivated during peak egg production as a result of increased stress or level of sex hormones at that time, leading to highest transmission to the progeny (Adair and Fitzgerald, 2008). Grafl *et al*. (2012) reported the outbreak of adenoviral gizzard erosion in commercial broiler flocks in Germany and found that the birds from all affected flocks originated from single broiler breeder flock and thereby highlighted the importance of vertical transmission.

**FOWL ADENOVIRUS DISEASES IN CHICKEN**

Fowl adenoviruses (FAdVs) are distributed worldwide and known to cause many important diseases in poultry like Inclusion body hepatitis (IBH), Hydropericardium syndrome (HPS), Hepatitis hydropericardium syndrome (HHS), Gizzard erosions (GE), Proventriculitis (PV), Tenosynovitis and respiratory infections.

**INCLUSION BODY HEPATITIS (IBH)**

Inclusion body hepatitis (IBH) in chickens was first reported during 1963 in the USA (Helmboldt and Frazier, 1963). The disease has a worldwide distribution, and there are indications that its incidence is increasing in many poultry industries (Mc Ferren and smyth, 2000). Classical IBH, affecting chickens at 3–5 weeks of age, is viewed as a sporadic disease with associated mortalities ranging from 0 to 15 per cent in broiler flocks. Inclusion body hepatitis was characterized by sudden onset of increased mortality, which might reach 10 per cent and occasionally be as great as 30 per cent (Adair and Fitzgerald, 2008). The clinical signs observed during FAdV infection were reduced feed intake, ruffled feathers, depressed appearance and inability to get up and walk and heavy mortality (Gaba *et al.,* 2010).Varying mortality from 2.75 to 11.66 per cent was noticed due to natural outbreak of IBH-HPS in different farms (Thakor *et al*., 2012). Almost all 12 serotypes of FAdV were incriminated in IBH (Chandra *et al*., 1998). Immunosuppressive diseases like infectious bursal disease (Fadly et al., 1976), chicken infectious anemia (Markowski-Grimsrud and Schat, 2003) and Marek’s disease (Niczyporuk *et al*., 2012) may play a role in the transmission of IBH and its increasing mortalities. Concurrent infection of fowl adenovirus with chicken infectious anaemia virus and avian leukosis virus was documented in India (Chitradevi *et al*., 2018). However, it has been recorded that IBH could induce independent mortalities without the presence of other immunosuppressive factors (Christensen and Saifuddin, 1989; Gomis *et al*., 2006; Ojkic *et al*., 2008). Nakamura *et al.* (2011) reported mortality rate of 1.2 to 17.0 per cent in broiler flocks with sudden death due to FAdV 2 infection without showing any clinical signs and occurred as primary diseases without involvement of other immunosuppressive diseases. Fowl adenovirus serotype 2, 4, 5, 6, 8 and 12 were reported in commercial broiler birds of natural outbreak of FAdV (Mittal *et al*., 2014). FAdV serotype 11was the predominant serotype associated with IBH from commercial broiler and broiler breeder recorded in 11 different states in India (Chitradevi *et al*., 2021). Affected flock showed enlargement of livers with friable texture, pin point or white necrotic foci and petechial haemorrhages with yellowish discoloration, congested kidneys and congested and oedematous lungs (Nayak *et al*., 1990; Balachandran *et al*., 1993; Sandhu *et al*., 1994; Kumar *et al*., 2013). Histopathological lesions of IBH were characterized by hepatic necrosis with microscopic eosinophilic or basophilic intranuclear inclusion bodies in hepatocytes (Kumar *et al*., 2006; Norina *et al*., 2016).

**HYDROPERICARDIAL SYNDROME (HPS)**

The first epidemic of HPS in broiler chicks was reported from Angora Goth near Karachi, Pakistan, in late 1987 (Jaffery, 1988; Khawaja *et al*., 1988; Cheema *et al*., 1989; Hasan, 1989) and subsequently recorded in Iraq (Abdul Aziz and Al Attar, 1991) and in India (Gowda and Satyanarayana, 1994). The HPS was an emerging and immunosuppressive disease of 3-6 week old broilers, with a characteristic rapid onset and spiking mortality reaching up to 60 per cent but more typically 10 to 30 per cent, with distinctive hydropericardium (Balamurugan and Kataria, 2004; Kataria *et al*., 2005). In chickens less than six weeks of age, the mortality usually varies from 2 to 40 per cent. Under certain conditions however mortality up to 80 per cent was recorded on the basis of the pathogenicity of the virus. Peak mortality was usually observed within 3 to 4 days followed by cessation within 9 to 14 days. Lethargy, huddling with ruffled feathers, loss of appetite along with yellowish mucoid droppings were noticed in birds clinically (Kataria *et al*. 2013). On post-mortem examination of affected birds showed clear, straw-colored watery or jelly-like fluid in the pericardial sac with the misshapen and flabby heart as well as haemorrhages on the heart muscles and other organs (Asrani *et al*., 1997; Kumar *et al*., 1997). Congestion and edema of lungs, enlarged, pale and friable liver, pale kidneys, and swollen bursa of Fabricius have been also observed (Cheema *et al*., 1989; Ganesh and Raghavan, 2000; Ahmad *et al*., 2011).

**GIZZARD EROSION (GE)**

Adenoviral gizzard erosion for the first time from a natural outbreak in a flock of layer chicken (Taimura *et al*.,1993). Gizzard erosions in broiler chickens as a result of FAdV 1 infections were reported in Japan and also in Europe (Okuda *et al*., 2001; Ono *et al*., 2001). Serotype 8 FAdV was isolated from gizzards exhibiting gizzard erosion in commercial broilers chicken in slaughter house (Ono *et al*., 2003). Affected chickens showed uneven growth, depression and dull feathers and the most severe lesions were located in proventriculus, gizzards and intestines (Okuda *et al*., 2004; Blicharz *et al*., 2011). Gizzard erosion outbreaks due to FAdV serotype 1 infections were reported in commercial broiler chickens in Japan, Europe, Korea ,Hungary and Sweden (Ono *et al*. 2001; Marek *et al*. 2010; Grafl *et al*.2013; Schade *et al*. 2013; Kajan *et al.*,  2013; Limdgren *et al*., 2022).Adenoviral gizzard erosions were characterized by low mortality but impaired growth and feed conversion resulting in economic losses (Schachner *et al*., 2016). Commercial layer birds affected with FAdV showed gizzard erosions and mortality (10 to 30 %), dullness, uneven growth, decreased feed and water intake and cause heavy economic loss (Bulbule *et al*., 2016). Fowl adenovirus serotype 2 and 3 was involved in causing gizzard erosions in commercial layer grower chicken in Tamil Nadu (Chitradevi *et al*., 2020).

**DIAGNOSIS**

Fowl adenovirus infection in chicken can be diagnosed based specific clinical signs, gross and histopathological lesions especially demonstration of intranuclear inclusion bodies (Trivedi *et al*.,2018). Electron microscopic demonstration of multiple aggregates of hexagonal adenoviral particles with basophilic intranuclear inclusions is successfully carried out for the detection FAdV (Ganesh *et al*., 2002; Bodewes *et al*., 2013). Laboratory diagnosis of is based on conventional and molecular techniques for virus detection. The Liver tissue is a target organ for FAdV replication and failure of the virus particles to develop in the hepatocytes could result in the failure of disease development in the FAdV infection in the chicks. Liver is the major organ identified for demonstration of HPS virus antigen and not demonstrated in other tissues (Ahmed *et al*., 1989). Virus isolation is carried out using different routes of embryonated chicken eggs McFerran and Smyth, 2000; Zhao *et al.,*2015). But not all FAdVs were multiplied in embryonated egg and cause recognizable lesions (McFerran, 1981). Virus isolation using primary chicken fibroblast, chick embryo kidney and chick embryo liver cell cultures are more sensitive for field fowl adenovirus isolation (Adair ,1978; Blicharz *et al.*,2011; Chitradevi *et al*., 2021). Molecular techniques such as polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP ) loop-mediated isothermal amplification (LAMP) and real-time PCR (Li *et al.*,  2017; Wang *et al.*,  2017; Schachner *et al.*,2018; Xie *et al.*, 2021).Hexon protein is the major surface protein of adenovirus, on which type, group and subgroup specific antigenic determinants were located (Russel, 2009). Hence hexon gene was selected for PCR amplification and detection of FAdV (Meulemans *et al*., 2001). Real time PCR and subsequent high resolution melting (HRM) curve analysis of three regions of the hexon gene were used for differentiating 12 FAdV reference serotypes (Steer *et al*., 2009).

**PREVENTION AND CONTROL**

Fowl adenoviruses are non enveloped in nature,highly resistance to inactivation by heat as well as other common disinfectant. The incidence of FAdVs infections can be reduced by maintaining good management and husbandry practices. Proper cleaning and disinfection, restriction of personnel movement, controlling the other concurrent infection and maintenance of proper ventilation is mandate for significant reduction of infection (Kataria et al., 2005). Many countries implement both live and inactivated vaccines to combat IBH and HPS/HHS. The FAdV serotypes 4 and 8 are most commonly used in commercial vaccines preparation (Saifuddin *et al*., 1990). To prevent and control the disease incidence in endemic areas, it is recommended that autogenous inactivated vaccines prepared from the prevalent serotype of FAdV be administered. In India, only inactivated oil emulsion vaccinations are used to prevent HHS, but only in suspected epidemic situations (Gowthaman *et al*., 2012). Kataria *et al*., (2005) reported an inactivated oil emulsified IBH-HHS vaccine made from fowl adenovirus produced in cell culture gave good protection. Similarly, Gupta *et al*., (2005) evaluated an inactivated vaccine against the HHS virus using chicken embryo kidney cell culture and found that the vaccine provided provided 100% protection in broiler chickens challenged with virulent FAdV−4. In India, currently multi adeno inactivated vaccine composed of FAdV-4, FAdV- 11 and FAdV – 8a and 8b are used against fowl adenovirus infection. In many other countries, inactivated vaccines are routinely used to vaccinate breeders and broilers along with strict biosecurity measures. When breeders are properly vaccinated, antibodies generated by the vaccine are transmitted to the progeny, providing protection against field infections and clinical disease number of unvaccinated birds. More recently, efforts towards improved immuno-prophylactic strategies are seen in the development of subunit vaccines, generated from recombinant capsid components of the virus. Schachner *et al*., (2014) reported development of recombinant vaccine for FAdVs-IBH and –HHS using fiber, penton and hexon genes.

**CONCLUSION**

In recent years, fowl adenovirus infection in chicken is considered as important emerging poultry disease, but the pathogenicity of most serotypes are still controversial. Concurrent infections associated with fowl adenovirus infection with other immunosuppressive viruses may increase the severity of infection in field. Timely diagnosis of various forms of fowl adenovirus infection among poultry based clinical and histopathological examination and molecular methods are inevitable. In breeder farms, strengthening of biosecurity measures and timely vaccination with updated serotypes are very important to control and prevent the infection.

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