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REVIEW ARTICLE

Avian Adenoviruses Infections with Special Attention to Inclusion Body Hepatitis/ Hydropericardium Syndrome and Egg Drop Syndrome

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ABSTRACT

The first avian adenovirus (AAV) associated with clinical disease was isolated from an outbreak of respiratory disease in quail in 1950 (Olson, 1950). Since that time, AAVs have been found in all types and breeds of chickens and from a variety of other avian species. The infections may be asymptomatic or associated with several clinical and pathological conditions. Vertical transmission via the egg is the most common way of transmission. Also horizontal transmission through faeces, contaminated egg trays, crates and trucks play a role in the infection route. Studies have demonstrated the presence of antibodies in healthy poultry, and viruses have been isolated from normal birds. Avian adenoviruses in chickens are the etiological agents of 2 diseases known as inclusion body hepatitis (IBH) and hydropericardium syndrome (HP). In some cases each condition is observed separately, however, recently the 2 conditions have frequently been observed as a single entity; therefore, the name hepatitis hydropericardium has been widely used to describe the pathologic condition. The syndrome is an acute disease of young chickens associated with anemia, haemorrhagic disorders, hydropericardium and high mortality.

Egg-Drop-Syndrome (EDS) is caused also by an adenovirus. The disease is characterised by a severe drop in egg production as well as the production of shell-less, thin-shelled, discoloured or misshapen eggs in apparently healthy birds. Ducks and geese are the natural host of the EDS virus. It was first described in chickens in the 1970s and spread to several countries world wide. The birds usually do not show any other signs of disease, and mortality is not expected. There is no specific treatment of the AAV infections. Active immunization by vaccination using an inactivated is wide spread.

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Etiology

The avian adenoviruses are non-enveloped DNA viruses. Adenoviruses are resistant to many several disinfectants and are relatively tolerant to heat and pH changes. Iodophor and aldehyde disinfectants seem to be effective if they are allowed to have contact to the virus for longer time. Composting infected chicken carcasses for 20 days completely inactivates the virus (Senne *et al*., 1994).

In the past the family *Adenoviridae* was divided by host range and antibody reactivity into two genera: the genus *Mastadenovirus* for viruses isolated from mammalian and the genus *Aviadenovirus* for viruses isolated from birds. Recently, the International Committee on Taxonomy of Viruses has divided the member of the family adenoviridiae in four genera (Benkő *et al.,* 2005). The ***Mastadenovirus*** genus contains the mammalian adenoviruses such as the human, simian, bovine, porcine, equine, murine, porcine, ovine and caprine adenoviruses. The genus ***Aviadenovirus***, formerly designated as group I avian adenoviruses (AAV), contains 11 of the 12 recognized European adenovirus serotypes classified into five (A to E) molecular groups and other related viruses. The genus ***Siadenovirus***, formerly designated as group II avian adenoviruses, includes the Haemorrhagic enteritis virus of turkeys (HEV), Marble spleen disease of pheasants (MSDV) and Avian adenovirus splenomegaly virus of chickens (AASV). The genus ***Atadenovirus***,

formerly designated as group III avian adenoviruses, includes the Egg drop syndrome virus (EDS) (Table 1).

According to Jensen and Villegas (2005) the nomenclature used for the serotypes of avian adenoviruses from chicken has created some confusion as different systems have been used in Europe and the U.S.; however, a revised nomenclature system has been published (Benkő *et al.,* 2005) that, if adopted, will clarify matters (Table 2).

Table 1: Classification of adenoviruses from birds (Smyth and McNulty, 2008)

Genus	Species	Serotype
Aviadenovirus	Fowl adenovirus A	FAdV-1
	Fowl adenovirus B	FAdV-5
	Fowl adenovirus C	FAdV-4
		FAdV-10
	Fowl adenovirus D	FAdV-2
		FAdV-3
		FAdV-9
		FAdV-11
	Fowl adenovirus E	FAdV-6
		FAdV-7
		FAdV-8a
		FAdV-8b
	Goose adenovirus	GoAdV-1
		GoAdV-2
		GoAdV-3
	(Duck adenovirus B)	DAdV-2
	(Pigeon adenovirus B)	PiAdV
	(Turkey adenovirus B)	TAdV-1
		TAdV-2
Siadenovirus	Turkey adenovirus A	TAdV-3
Atadenovirus	Duck adenovirus A	DAdV-1

Table 2: Classification of fowl adenoviruses (Jensen and Villegas, 2005)

Species	Serotype number			Proposed type strains	
	Europe	USA	ICTV	Europe	USA
A	1	1	1	CELO	QBV/Phelps
B	5	8	5	340	M2/Tipton
C	4	4	4	KR5	J2
C	11	10	10	C2B	C2B
D	2	2	2	GAL-1	P7
D	3	3	3	SR49	--
D	10	9	9	A2	A2
D	12	12	11	380	--
E	6	5	6	CR119	--
E	7	11	7	YR36/X11	X11
E	8	6	8a	TR59	T8
E	9	7	8b	764	B3

Inclusion body hepatitis (IBH)/Hydropericardium syndrome (HPS)

IBH was first described in 1963 in the USA (Helmboldt and Frazier, 1963). Then after, the disease has been reported in many countries worldwide. It is a sporadic disease condition caused by several serotypes of fowl adenoviruses (Fitzgerald, 2008; Smyth and McNulty, 2008).

In 1988, a new broiler disease was reported from Angara Goth near Karachi in Pakistan and called as Angara Disease. The clinical signs and the course of the disease were similar to IBH. The main pathological findings were the accumulation of a clear, straw coloured fluid in the pericardial sac, therefore the disease was called **Hydropericardium Syndrome** "HPS" (Jaffery, 1988). The disease has subsequently been recorded in Iraq (Abdul-Aziz and Al-Attar, 1991), India (Gowda and Satyanarayana, 1994), Mexico, Ecuador, Peru, Chile (Voss *et al.*, 1996; Toro *et al.,* 1999), South and Central America (Shane, 1996), Slovakia (Jantosovic *et al.*, 1991), Russia (Borisov *et al.*, 1997) and Japan (Abe *et al.*, 1998). An adenovirus was detected and later isolated (Rabbani and Naeem, 1996; Voss *et al.,* 1996; Mazaheri *et al.,* 1998; Singh *et al.,* 2002). The inclusion body hepatitis/hydropericardium syndrome (IBH/HP) has been reported to occur in both broilers and layers (Cowen, 1992). It seems that immunosuppression, prior to or concurrently with a FAdV infections, is necessary to develop IBH. Infectious bursal disease virus (IBDV), chicken anaemia virus (CAV) and mycotoxins are known to increase the pathogenicity of FAV infections (Rosenberger *et al.,* 1975; Fadly *et al.,* 1976; Bülow *et al.,* 1986; Toro *et al.,* 2000; Shivachandra *et al.,* 2003). However, several cases of IBH occurred without obvious influence of infectious immunosuppression (Reece *et al.,* 1986; Christensen and Saifuddin, 1989). On the other hand, Zavala *et al*. (2002) infected 1-day-old grandparent meat-type chickens carrying maternal antibodies against FAV with a field isolate of FAV associated with inclusion body hepatitis in broilers, avian leukosis virus subgroup J ALV-J, or both FAV and ALV-J and they found no significant differences in the dually infected birds in comparison with chickens that received a monovalent challenge with either FAV or ALV-J.

The infection is transmitted by vertical and horizontal means. Vertical transmission is reported as an important feature of fowl adenovirus (FAV) to spread from parent birds to progenies (McFerran and Adair, 1977; McCracken and Adair, 1993). Infected breeder shed virus to their progeny for three to six weeks until development of immunity occurs (Toro *et al*., 2001; Mazaheri *et al*., 2003). There is evidence that adenovirus infections can become latent and that periods of stress, such as the onset of egg production, will reactivate viral shedding (Girshick *et al*., 1980). Fadly *et al.* (1980) reported that there is evidence that adenovirus infection can remain latent and undetected for at least one generation in a specific-pathogen-free flock.

The bird-to-bird transmission of the virus in a flock occurs horizontally by the oral-faecal route and further spread take place by mechanical means and by contamination with infected faeces. Commercial hatching eggs may be a mechanism of spread of AAV from one country to another (Cook, 1974; Ahmad *et al.,* 1992; Akhtar *et al.,* 1992; Akhtar, 1995; Adair and Smyth, 2008a).

Mazaheri *et al.* (1998) tested the pathogenicity of FAV serotype - 4 isolated from typical field cases of hydropericardium syndrome in Pakistan and Ecuador in one day old specific pathogen free (SPF) chicks. Infected chickens as well as their contact sentinels, showed depression and reduced flight reactions between day 6 and 11 p.i. After this period no further clinical signs were seen. Mortality commenced 7 days p.i. and continued for 5 days. It was impossible to isolate adenovirus from the livers from any killed chick at 3 days p.i.. Isolation of virus was possible from the liver of following oral infection of 1-day-old chicks with purified field isolates.

Under field condition the disease is characterized by sudden onset of mortality in chickens < 6 weeks old and as young as 4 days of age. Mortality normally ranges from 2-40 percent, especially when birds are < 3 weeks of age. However, there have been outbreaks in which mortality has reached 80 % depending on the pathogenicity of the virus, immune status of the chicks and concurrent secondary infections. Mortality generally peaks within three to four days and ceases within 9-14 days. Clinically the birds showed lethargy, huddling with ruffled feathers, inappetence and yellow, mucoid droppings may be seen. The infection can be accompanied with bad feed conversion and a reduced weight gain (Anjum *et al.*, 1989; Cowen, 1992).

Gross lesions include an enlarged pale and friable liver sometimes with necrotic foci, also ecchymotic haemorrhages may be present in the liver and less consistently ecchymotic haemorrhage can be observed in leg and breast muscles (Howell *et al*., 1970, Macpherson *et al.*, 1974; McFerran and Adair, 1977). The heart can be flabby with a mild hydropericardium. In case HPS a straw-coloured transudate is present in the pericardial sac (Anjum *et al.*, 1989). In addition, nephritis, enlarged spleens and thymus atrophy could be observed in most dead birds. Histopathological lesions include necrotic focal lesions and some of the livers had basophilic intranuclear inclusion bodies. Haemorrhages under the epicardium with multifocal necrosis in the myocard are the major findings in the hearts and lymphoid depletion of spleen, thymus and bursa of Fabricius could be observed (Ahmad *et al.*, 1989; Gowda and Satyanarayana, 1994). The liver showed histological changes, such as small multifocal areas of coagulative necrosis, mononuclear cell infiltration and the presence of basophilic inclusion bodies in the hepatocytes surrounded by a clear halo or filling the entire enlarged nucleus (Kumar *et al.*, 1997; Nakamura *et al.*, 1999).

Egg drop syndrome (EDS)

EDS is a disease characterized by a drastic drop in egg production as well as the production of abnormal eggs in apparently healthy chickens and quails. The disease was firstly described in 1976 by Van Eck *et al*. (1976) in The Netherlands. Thereafter, the disease was observed in several countries around the world including France (Picault, 1978), Great Britain (Baxendale, 1978), Northern Ireland (McFerran *et al.,* 1978), Belgium (Meulemans *et al*., 1979), Hungary (Zsák and Bartha, 1979), Israel (Malkinson and Weisman 1980), Australia (Firth *et al*., 1981), Japan (Yamaguchi *et al*., 1981), Singapore (Singh and Chew-Lim, 1981), Taiwan (Lu, *et al*., 1985), South Africa (Bragg, *et al*., 1991), India (Kumar *et al*., 1992), China (Zhu and Wang, 1994), Bolivia (Bishop and Cardozo, 1996). The antibody to the virus was demonstrated from chickens in Denmark (Badstue and Smidt, 1978), Brazil, (Hwang *et al*., 1980); Mexico (Rosales *et al*., 1980), Nigeria (Nawathe and Abegunde, 1980), USA (Calnek, 1978), Germany (Kaleta *et al.*, 1980) and New Zealand (Howell, 1982).

The initial outbreak in chickens was probably caused by a contaminated vaccine grown in duck embryo fibroblasts, since antibodies to EDS virus have been detected in the sera of duck, geese, and herring gulls prior to 1975 (Bartha *et al.*, 1982) i.e. before the diseases was recognized in hens (McFerran, 1979). In addition, the EDS outbreaks were observed in the quail flocks reared together with infected chickens and resulted in the fall of the egg production and in the increase of number of soft-shelled eggs (Das and Pradhan, 1992).

In spite of the fact that the disease outbreaks were mostly recorded in laying hens only and some time in quails, EDSV or the antibodies against the virus have been detected in ducks and geese (Schlör, 1980), pheasants, guinea fowls (Zanella *et al*., 1980), pigeon (Durojaiye *et al*., 1992) and in wild birds (Malkinson and Weisman, 1980).

In 2001, EDSV showed to cause a severe acute respiratory disease of the young goslings in Hungary. The disease affected goslings between 4 and 20 days of age. The symptoms included anorexia, depression, sneezing, coughing, dyspnoea, and rales (Ivanics *et al*., 2001). Recently, Biđin *et al*. (2007) reported on a naturally occurring EDS in turkey breeder flocks in Croatia, which were accompanied with a significant decrease in both egg quality and production.

The disease caused is by duck adenovirus a member of genus *Atadenovirus*. The virus has haemagglutination activity and has its reservoir in ducks and geese. The complete nucleotide sequence data revealed that it is an intermediate virus between mammalian and avian adenoviruses (Hess *et al*., 1997).

EDS virus transmits vertically from hens to chicks and also horizontally from chicken to chicken (Cook and Darbyshire, 1980 and 1981; Darbyshire and Peters, 1980). Contaminated eggs as well as egg trays or faeces seem to be the main sources for virus spread (Smyth and Adair, 1988). However, some outbreaks have been attributed to contact with wild birds or water contaminated by feces from wild birds.

Smyth *et al*. (1988) carried out an investigation on the pathogenesis of EDS in laying hen. After experimental infection viral antigen and intranuclear inclusion bodies were detected in the surface epithelium of the nasal cavity of conventional hens 2 to 6 days p.i. Low levels of viral antigen were detected in lymphoid tissue throughout the body 2 to 5 days p.i. and inflammatory lesions and viral antigen were observed in the infundibulum 3 to 5 days p.i.. Viral replication was first detected in the pouch shell gland (PSG) 8 days p.i.. Viral antigen was never detected in the surface epithelium of the alimentary tract.

The disease is most severe in broiler breeders and brown egg layers. White layer lines are less affected (Butcher *et al*., 1999). The mortality is usually negligible. Birds infected vertically can remain asymptomatic until the bird become sexually mature. The first sign of abnormality is the production of eggs with shells that are paler and thinner than normal, and then a rapid change to the production of soft shelled and shell-less eggs. No shell irregularities considered typical for IB infection, such as abnormally-shaped eggs or eggs with ring-like or rough surfaces. The thin albumen of the shell-less and soft-shelled eggs is always watery and not ropy, in contrast to that of normal eggs. There is always a definite demarcation between the thick and thin albumen. In many instances the thick albumen shows a general turbidity or streak-like cloudiness. Total egg production dropps in

many outbreaks to levels lower than half the pre-disease level. Subsequently, flocks gradually resume production to levels that could be considered normal for birds. Outbreaks lasted approximately 3 to 8 weeks (Van Eck, 1976; McFerran *et al.*, 1978).

Although signs of EDS are quite characteristic, diagnosis must not be made on the clinical picture alone but should be confirmed by laboratory tests, since several infectious and non infectious causes can cause drop in egg production and might impair the external as well as internal egg quality. Examples are infectious bronchitis (IB), Newcastle disease (ND), avian encephalomyelitis (AE), fowl pox, infectious laryngotracheitis (ILT), avian metapneumovirus (AmPV), Mycoplasma gallisepticum (MG), and Mycoplasma synoviae (MS). Among the parasites, nematodes (Ascaridia, Capillaria, and Heterakis) may be responsible for egg drops. In addition several non-infectious factors such as stocking density, management and quality of feed and water are involved in egg production failures and should be considered (Meulemans, 1993; Gupta, 2008; Feberwee *et al*., 2009)

At necropsy there is no specific lesion, but a slight atrophy of ovary and oviduct can be observed. Histopathological changes can be seen in the oviduct and uterus (shell gland). There may be severe degeneration and desquamation of the epithelial cells, atrophy of the uterine glands and infiltration of heterophils, lymphocytes, and plasmacytes. Intranuclear inclusion bodies may be found in the epithelial cells of the uterus, isthmus, and vaginal gland region (Adair and Smyth, 2008b; Smyth and McNulty, 2008).

Diagnosis of Adenovirus infections

The diagnosis of poultry diseases in less developed regions of the World is generally based upon case history, clinical signs and post-mortem examination as important steps toward disease diagnosis, but it should not be the final step. In most cases clinical signs and lesions of many diseases are similar and laboratory tests are required to identify the specific cause (Fig. 1).

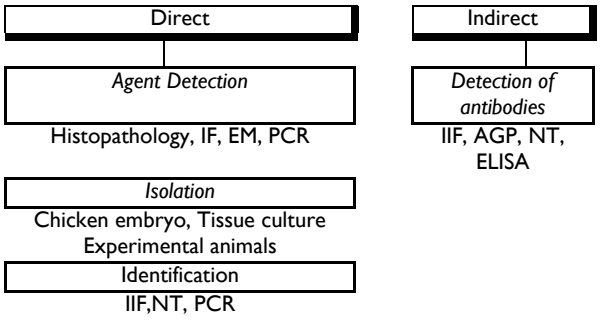

Fig. 1: Laboratory diagnosis of poultry diseases

The laboratory diagnosis can be applied to direct detection as well as for isolation and identification of the causative agent or indirectly to detect antibodies (Hafez and Hess, 1999). The diagnosis of adenovirus infections in poultry is in most cases based on histological investigations and detection of intranuclear inclusion bodies in hepatocytes or on detection of the antigen or virus particles using Immunofluorescence test or electron microscopy. In the last few years several molecular biological tools such as PCR, Real-time PCR and REA were developed allow the detection of the Virus – DNA as well as the further identification and typing of adenoviruses (Erny *et al*., 1991; Raue and Hess, 1998; Hess *et al*., 1999; Hess, 2000; Raue *et al*., 2002; Lüschow *et al*., 2007; Steer *et al.*, 2009).

However the isolation of the **aviadenoviruses** using chicken embryo liver (CEL) cell culture and chicken embryo fibroblast cell culture with further identification and determination of the pathogenicity seems to be very important, since the pathogenicity of the isolates within the same serotype can be widely differ. The cross neutralization tests and /or molecular biological tools are necessary to serotype the isolated virus and to determine a new serotype (McCracken and Adair, 1993; Kumar *et al.*, 2003; Lüschow *et al*., 2007; Steer *et al.*, 2009).

EDSV can be isolated in embryonated duck or goose eggs, and in cell cultures. Susceptible cell lines include duck and chick embryo liver, duck kidney, and fibroblast cells. Also isolation has been made in chicken embryo kidney or liver cells (Adair et al., 1979). The virus may be isolated directly from the reproductive tract of affected hens. Alternatively, abnormal eggs may be fed to naive hens; virus isolation is attempted from the shell gland of these hens when they produce abnormal eggs (McFerran and Adair, 2003).

The most common serologic test is the immunodiffusion test that detects the group specific antigen. This test is not sensitive enough. A group specific ELISA and IIF tests are more sensitive. The serum neutralization test has been used to detect serotype-specific antibody but is labour intensive and expensive. In general the interpretation of serologic tests is difficult because antibodies against AAVs can be found in both healthy and diseased birds (McFerran and Adair, 2003).

In addition for the detection of antibodies against **EDSV** haemagglutination inhibition using fowl RBC can also use. Dhinakar Raj *et al*. (2007) developed immunofiltration (flow through) test to detect the presence of antibodies to egg drop syndrome 76 (EDS) virus in chicken sera and compared it with HI and ELISA. In total, the immunofiltration test could detect EDS antibodies with a sensitivity and specificity of 90.14 and 92.86%, respectively as compared to the HI test. Compared to ELISA, the sensitivity and specificity of the developed immunofiltration assay was 79.45 and 94.58%, respectively. The disadvantage of this test is the qualitative detection of antibodies in the serum, which may not be highly informative on all occasions and this test can be used as a preliminary test before confirmation can be done by another more sophisticated laboratory based assay.

Control of Adenovirus infections of poultry

Control of IBH/HPS

Biosecurity practices are the primary and essential step to prevent the infection. The proper management, cleaning and disinfection of premises and equipment, restricted entry of visitors and vaccination crews in the poultry houses play a significant role in prevention of the disease. However, in countries with high infectious

pressure the disease has been brought under control by formalin-inactivated vaccines prepared from liver homogenates from infected birds or by inactivated cell culture – derived (Shane, 1996, Kumar *et al.*, 1997; Kataria *et al.*, 1997; Balamurugan and Kataria, 2004).

Roy *et al.* (1999) compared two inactivated vaccines prepared from the liver of experimentally infected chickens. One was prepared without adjuvants described by (Afzal and Ahmed, 1990). For the 2nd one, liquid paraffin was used as adjuvants after chloroform extraction and inactivation with formalin. The oil emulsion vaccine applied subcutaneously at 10th day of age provided 100% cent protection up to seven weeks of age against challenge. The inactivated vaccine without adjuvant was less efficacious. In a similar study by Afzal and Ahmed (1990), owing to the poor performance of a similar vaccine, they suggested that birds should be vaccinated twice at 10 and 21 days of age. In the field trial, the oil emulsion vaccine was highly effective; there were no deaths due to hydropericardium syndrome and birds were sold to the market at eight weeks.

Balamurugan and Kataria (2004) review the experiences of several authors using the vaccines to control HPS in poultry. In two field trials, involving 570 000 birds on 128 farms, the overall mortality ranged from 0.77 to 3.8% in vaccinated and from 11.11 to 30% in unvaccinated birds (Ahmad *et al*., 1990). In another trial, the mortality in vaccinated birds was 0.52% compared to 5.34% in unvaccinated birds kept on the same premises. Vaccination was also effective when carried out in the face of an outbreak; mortality in the vaccinated infected birds being 2.33% compared with 10.27% in unvaccinated infected birds (Afzal and Ahmad 1990). Inactivated chicken liver cell culture and embryonated egg-propagated vaccine used subcutaneously at $10^{3.5}$ LD_{50}/dose/bird provided protection against challenge with 1 ml of a 20% liver homogenate at a biological titre of 2×10^5 LD_{50}/0.5 ml (Naeem *et al.*, 1995a, b). Shane (1996) evaluated five inactivated vaccines used in Mexico. Complete protection, with an absence of histological changes in chicks challenged with $10^{3.5}LD_{50}$ of the DCV-94 adenovirus strain, was observed. Icochea *et al*. (2001) evaluated the efficacy of three inactivated vaccines against IBH/HPS in Peru in two different experiments and concluded that the protective effect of a commercial oil-adjuvant cell culture IBH vaccine was superior to the autogenous vaccines and that the mortality rates were not dose-dependent. As most cases of IBH are the result of vertical transmission, vaccines have been proved to be highly successful at controlling IBH by preventing vertical transmission and inducing maternal immunity (Toro *et al*., 2002; Alvarado *et al*., 2007). Toro *et al*. (2002) reported that effective protection of the progeny of chickens against IBH-HPS could be achieved by dual vaccination of breeders with FAV-4 and CAV.

Alvarado *et al*. (2007) isolated pathogenic adenovirus, identified as Stanford strain and characterized as European serotype 9. The level of protection against IBH was evaluated in two broiler-breeder progenies from AAV 8/11– vaccinated grandparent flocks and a commercial broiler flock by challenge at 1 or 7 days of age with the AAV 8 and 11 serotypes and/or the Stanford strain. The broiler-breeder progenies and the commercial broiler flock exhibited protection against IBH after challenge. They conclude that broiler-breeder progenies from 30- to 50-wk-old grandparents vaccinated with the AAV 8/11 vaccine were adequately protected against challenge with the AAV 8 and 11 serotypes and the Stanford strain (serotype 9).

Control of EDS

Beside biosecurity, vaccination with an inactivated vaccine prior to lay is mostly important to prevent egg production losses and reduced egg shell quality in commercial layer and breeder flocks. Initial vaccination occurs between 14 and 16 weeks of age. However, vaccination cannot completely inhibit virus excretion in feces, but decrease virus shedding (Heffels *et al*., 1982).

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