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NDV Epidemiology and Pathogenesis in Poultry: Current Status and Emerging Perspectives with Special Reference to Situation in Egypt

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ABSTRACT

Newcastle disease (ND) is a serious infectious disease of bird species triggered by Avian Orthoavula virus 1 (AOAvV-1) which was previously called ND virus and it infects more than 200 poultry types. The disease is highly devastating in susceptible bird species. In Egypt, despite the application of colossal vaccinations for controlling ND since several decades, the illness remains one of the most destructive diseases that impacts enormous chicken farms. Continuous mutations of NDV have led to twenty genotypes, and genetic variation could cause disease epidemics in previously immunized birds. Recently, NDV genotype VII (NDV GVII) become the source of the current epidemics all over the world including Egypt. One of the most critical features for NDV control is a thorough understanding of the pathophysiology of NDV particularly genotype VII in various poultry species. This review sheds light on some important aspects of the epidemiology and pathogenesis of NDV in general and NDV GVII especially.

Keywords: Avian Orthoavula virus 1, Birds, NDV GVII, Virulence.

INTRODUCTION

Newcastle disease virus (ND) is caused by avian ortho avulavirus 1 (AOAvV-1) which was previously called Newcastle disease virus (NDV) (Lamb, 1996). It is an extremely contagious and fatal viral disease that affects several avian and non-avian species causing terrible losses (Chen et al., 2013; Sharma et al., 2012). NDV affects more than 200 different poultry species with different forms of diseases (Alexander et al., 2012). ND is a reported viral infection and the highest prevalent indigenous viral disease following avian influenza, worldwide (Zanaty et al., 2019b). NDV belongs genus Ortho avulavirus and Avulavirinae subfamily of the family *Paramyxoviridae* (ICTV, 2022). Despite widespread vaccination regimens in chicken industries. Efforts to successfully manage the disease still have only patchy results (Radwan et al., 2013).

History of Newcastle disease and current status in Egypt:

In 1926, NDV infection was detected in England and Indonesia (Alexander et al.,

2012). According to the history of NDV infection, there are four significant epidemics of NDV. The first panzootic of the disease developed by viral class II genotypes II, III, and IV (Ballagi-Pordany et al., 1996). The second panzootic could be caused by genotype V and spread across different places of the globe (Herczeg et al., 1999). The third panzootic was triggered due to NDV class II genotype VI (Czegledi et al., 2002). The fourth epidemic was probably caused by the widespread NDV genotype VII (Liang et al., 2002).

In Egypt, the detection of NDV infection was confirmed in 1948 (Daubney and Mansy, 1948), and from that time, catastrophic NDV outbreaks have been recurrently stated in Egyptian field (Mohamed et al., 2009). Currently, the main NDV genotypes circulating in Egyptian poultry farms are genotypes II, VI, and VII (El Naggar et al., 2018; Sabra et al., 2017; Selim et al., 2018). The NDV GVII is the prevalent one. It was stated at a rate of 37.8% in 2014-2015 (Awad et al., 2015), 57.5% in 2012-2015 (El-Bagoury et al., 2015), and 45.46% in 2019 (El-Shall et al., 2015).

Locality	**Prevalence**	**Diagnosis**	**Reference**
Sharkia Dakahlia Gharbia Sohag Port-said Alexandria Assiut North and South Sinai Damietta Cairo Ismalia Suez	Domestic birds (chickens, ducks, Turkey, and pelicans): 57.4% chicken: 65% duck: 47.4% Wild birds (Hooded crow, Common gull, little curlew, Brown quail, European turtle dove, Black-crowned night heron, Common moorhen, Cattle egret, Mallard duck, Wedge-tailed shearwater, Northern Shoveler, Grey heron, purple gallinule (African swamphen), American pipit): 72.9%	Virus isolation NDV F gene-specific RT-PCR NDV M gene-specific RT-PCR	(Eid et al., 2022)
Egypt	domestic poultry (chickens and Turkey): 52.4%	Virus isolation NDV F gene-specific RT-PCR	(Abozaid et al., 2022)
Damietta Port Said Matruh	wild birds (Northern shoveler, pintail, laughing dove, teal, wigeon, moorhen, mallard and coot): 3.77%	semi-nested RT-PCR assay	(Hasan Mohammed et al., 2020)
Al Behera Al Daqahlia	13.4% 13.0%	Virus isolation Intra-cerebral	(Zanaty et al., 2019a)

Al Fayoum Al Gharbia Al Giza Al Minia Al Monofiya Cairo Al Qaliobia Al Sharqia Alexandria Beni-Sueif Ismailia Kafer Alsheikh North Sinai Port Said Qena Matrouh	33.8% 14.3% 24.3% 10.0% 0.0% 13.3% 0 0.0% 14.0% 11.1% 9.1% 19.4% 16.7% 14.3% 100.0% 0.0% 0.0%	pathogenicity index (ICPI) rRT-PCR using genotyping primers	
El Behera Alexandria El Gharbia El Qaliobia El Dakahlia Kafer ElShiekh El Menofia El Giza Marsa Matrouh El Sharkia	41.2% 30.7% 53.3% 22.2% 42.8% 66.6% 66.6% 0% 50% 50%	Virus isolation intra-cerebral pathogenicity index (ICPI) full-length F protein nucleotide sequences	(Abd El-Hamid et al., 2020)
Giza Gharbiya Kalyobiya Sharkia Menofia Fayoum Minia	Chickens: 57.5 %	Virus isolation Mean death time (MDT) intra-cerebral pathogenicity index (ICPI)	(El-Bagoury et al., 2015)

NDV classification and nomenclature:

ND originates by velogenic strains of AOAvV-1, which is a member of Avulavirus of the sub-family Avulavirinae of the *Paramyxoviridae* family. ND-virus is recently termed Avian-ortho avulavirus-1 (AOAvV-1) (ICTV, 2022). Although all AOAvV-1 strains belong to the same serotype, there are several distinct ways to classify them genetically (E. W. Aldous 2003; ICTV, 2022). To categorize NDV strains, two systems of classification based on NDV genomic lengths and either entire or part sequencing for the Fusion gene were used. The first was proposed by Aldous, who classified NDV strains into 6 lineages & thirteen sub-lineages, with the addition of three more sub-lineages later (Miller et al., 2010b). The second categorization divided AOAvV-1 strains into two clades. Class I clade was more subdivided into nine genotypes (1 to 9) (Kim et al., 2007b). Class II clade was classified into 11 genotypes (I-XI)

(Maminiaina et al., 2010; Miller et al., 2010a). Dimitrova et al. additionally, updated and unified the phylogenetic classification system for NDV; they kept class I and class II classification. But they added three genotypes more in class II and decreased the number of sub-genotypes (Dimitrov et al., 2019).

AOAvV-1 GVII detected in Egypt in the year 2011 and is thought to be the source of the current outbreaks. Despite the consistency with which vaccination programs are implemented all over the world, genotype VII NDV remains a severe danger to the poultry industry (Manar AA Khader1, 2020). Initially, AOAvV-1 GVII was begun in the Far-East then separated into two sub-genotypes: VIIa, which expanded to Europe and Asia, and VIIb, that reached South Africa. VIIc, d, and e are sub-genotypes that were detected in China, Kazakhstan, and South Africa, and VIIf, g, and h were present in Africa (Ewies et al., 2017).

Regarding NDV isolates pathogenicity, NDV isolates are categorized into different pathotypes: Apathogenic NDV strains (avirulent with entero tropism); Lentogenic strains (only with mild respiratory disease); Mesogenic strains (moderate-virulent produce respiratory lesions and deaths in chicks of age less than eight weeks); and Velogenic strains (cause systemic infections with high mortalities) (Miller and Patti, 2013). Velogenic strains are more subdivided into velogenic viscerotropic (causing severe digestive system infection) and velogenic neurotropic (cause severe nervous system infections) (Susta et al., 2011).

NDV structure and genome organization:

NDV genome is a negative-sense, single stranded RNA (Samal et al., 2012), It consists of 15,186 nucleotides (nt) (Sanz-Ramos et al., 2008), 15,192 nt (Huang et al., 2004a) or 15,198 nt (Russell and Alexander, 1983). It has 6 ORF (open-reading frames) that encodes six basic and two additional proteins (Cattoli et al., 2011). The structural proteins are arranged in the direction three to five; as follow, nucleo-protein (NP), matrix-protein (M); fusion-protein (F); haemagglutinin-neuraminidase (HN) and large RNA polymerase (L) (Czegledi et al., 2006; Kumar et al., 2011). Moreover, the Phosphoprotein gene produces two additional proteins (W & V) when mRNA is translated at the editing site by guanine addition.

Bossart et al. (2009) define HN as a homotetrameric membrane protein of type II with its N-terminus inserted into the envelope (Bossart et al., 2009). The ectodomain, which comprises two essential components, comes after the first transmembrane domain. 1) mutations in the stalk region and transmembrane, which change the protein's structure and activity, particularly its interaction with homologous F-protein, which impacts the protein's fusogenic effect. 2) At the C-terminus, a large globular head domain containing the key amino acid sequences that regulates the sialic acid receptor binding and other related activities (Jihui Jin, 2016; Liu et al., 2019). HN has a molecular weight (MW) around 53 KDa (Tan et al., 1995). HN gene is around 2000 nt long and comprises an ORF that encodes 571, 577, 581, or 616 amino acids (Sakaguchi et al., 1989; Tan et al., 1995). The major of them, HN-precursor 616 (found in low virulent strains), may be changed into a functional HN protein by proteolytic cleavage of 45 residues from the C-terminus of the HN-precursor (Sakaguchi et al., 1989). The remaining 3 translations, 571, 577, and 581 amino acids, are already active and are often encountered in velogenic strains (Yusoff et al., 1997). As a result, the sequence of the HN protein may reflect NDV pathogenicity.

F-protein is a type 1 integral membrane protein, has 553 amino acids with a MW of 55 KDa (Romer-Oberdorfer et al., 2003). A homotrimeric glycoprotein, the F-protein, is composed of three monomers coming together. Within each oligomer, distinct domains, including the head, neck, and stalk, can be identified. The head and neck domains house both the F2 and F1 polypeptides. The stalk region, constituting a lengthy coiled-coil trimer, includes the carboxy terminal part of heptad repeat domain 1 (HR1). This HR1 section is vital for the fusing function of the F-gene (Morrison, 2003). F- proteins of paramyxoviruses also had a cytoplasmic tail (CT) and a transmembrane domain (TM). The CT is thought to have been implicated in fusing function, even though the TM is obviously required to attach the protein in the membrane (Gravel et al., 2011). The F1 polypeptide's amino terminus contains the major functional site, which is a hydrophobic stretch of amino acids (aa, 117-142) known as the fusion peptide (Morrison, 2003; Teng et al., 2019). On the basis of comparisons to the Sendai virus, a second fusion peptide with an internal position in F1 polypeptide was reported within paramyxoviruses (Ghosh et al., 2000; Peisajovich et al., 2000). Four additional heptad repeat (HR) domains were reported in the NDV F-protein and believed to be involved in both the fusion activity and the F-protein folding (Morrison, 2003).

Matrix (M) protein is made up of 346 amino acids and has a MW around 40 kDa. It is an essential protein that has multiple conserved hydro-phobic sites (Seal et al., 2000a; Williams and Dillard, 1968). N protein is a polypeptide protein, of 489 amino acids and MW 53 KDa (Kho et al., 2001). Phospho-protein protein has a MW about 42 KDa and it contains 395 amino acids (Yusoff and Tan, 2001). L protein, with a mass of 249 KDa and 2204 amino acids, is the biggest and least frequent of the AOAvV-1 basic proteins (Yusoff et al., 1987).

Role of NDV proteins in virus pathogenesis and replication:

HN protein

The HN is a surface glycoprotein, it delivers multifunction. It binds sialic-acid (Sia) ligands during virus attachment to susceptible cells and degrades Sia ligands from progeny viral particles (neuraminidase activity (NA)) to prevent viral self-aggregation (Phale, 2018; Ruan et al., 2020). It also endorses fusion of the membranes via how it interacts with F-protein, enabling RNA to enter the cell. HN protein's main functional domain has two sites for the binding to receptor. The first one is crurial in Sia-receptor interaction and Neuraminidase activities, while second is related to binding to receptor and fusion while has no effect on the neuraminidase activity (Mahon et al., 2011). Therefore, HN protein has an essential function in viral pathogenicity and tissue tropism (Yusoff and Tan, 2001).

Fusion protein structure and its function

It is initially made and glycolyzed in the endoplasmic reticulum in the inactive form (F0) (Nagai et al., 1989) that needs to be activated with specific proteolytic enzymes within the Golgi apparatus resulting in two disulfide-linked components F1 and F2 (Gravel & Morrison, 2003). Because F0 cleavage alone is insufficient for fusion, HN protein is also required (Smith et al., 2009). The F0 cleavage site is positioned between 112 and 117 amino acids (Bossart et al., 2009).

The differences in tropism and virulence detected in NDV strains depends on the presence of cellular proteases essential for viral (F0) activation (Nagai, 1993). The F0 of high and moderate virulent AOAvV-1 strains have a multi-basic amino acid

cleavage site (^{112}R/K-R-QR/K-R-F^{117}) which permits cleavage by ubiquitous intracellular proteases found throughout the body leading to pantropic infection (Garten et al., 1980; Nagai, 1993). In contrast, the AOAvV-1 lentogenic strains having a mono-basic motif (^{112}G/E-K/R-Q-G/E-R-L^{117}) at the site of cleavage of F0 could be only cleaved by specific extracellular trypsin-like proteases confined to specific organs like respiratory and digestive systems (Kommers et al., 2003b). The difference in the mode of cleavage of F0 explains the high tissue invasiveness of AOAvV-1 virulent strains (Smith et al., 2009).

Matrix protein

It is located on the internal surface of the virus envelope, which is considered a third NDV envelope protein. It is linked to the HN gene amino terminus (Li et al., 1980). In general, the NDV matrix gene has a multifunctional role in the virus replication cycle (Duan et al., 2019). It is involved in viral protein-protein interactions, such as the (NC) nucleocapsid and cytoplasm regions of the HN and Fusion proteins. In additions, it enhances RNP compacting mainly during the virus's assembly and budding phases during replication (Iwasaki et al., 2009; Leeuw and Peeters, ,1999). It suppresses the replication of host cell genes by preventing mRNA exportation (Kopecky and Lyles, 2003). So, it is considered nucleocytoplasmic shuttling protein. It has been seen to be concentrated in a nucleus early in infection, then gets linked with and persists in nucleoli during infection. The nuclear-nucleolar localization of the M protein regulates an equilibrium between the transcription and replication of viruses (Peeples et al., 1992; Yu et al., 2016). t organizes the development and infecting process in both location and time, helping to alter the sequence of events during the budding and fusing processes (Duan et al., 2019).

Nucleoprotein

The NP protein forms with RNA viral nucleocapsid, which promotes the replication and transcription of the virus and shields the virus's genetic material against nuclease activity (Kho et al., 2003). NP is found in high proportion in virions and provides core helical nucleocapsid shape of the virus. It is a highly immunogenic protein, and is the major regulator in viral genome replication (Abdisa and Tagesu, 2017).

Phosphoprotein

It forms a different combination with the nucleo-protein and large polymerase proteins and the nucleocapsid. P-L complex has an important role in transcription of viral genome as it is a polymerase co-factor, and phospho-protein holds the function of the P-L complex's binding to the NC. P protein delivers NP to the nascent RNA after sufficient viral proteins are produced (Dortmans et al., 2010b). In additions, it thought that the NP-P complex adjusts the modifications from transcript to replication (Hamaguchi et al., 1985). V and W are two non-structural proteins that are produced from the P gene by transcription modification. They have an important role in virus pathogenicity by interference with cellular antiviral proteins (Gotoh et al., 2001).

RNA-dependent RNA polymerase protein

The L protein, in collaboration with P and N proteins, performs all viral polymerase's catalytic functions related to transcription and replication (Fields, 2007). During replication cycle, large polymerase protein serves as an RdRP (RNA-dependent RNA polymerase) along with a viral replicase and transcriptase. In additions, it has an important role in posttranscriptional modification processes, e.g., capping,

methylation, and polyadenylation of mRNAs (Dortmans et al., 2010b).

V and W proteins (Accessory proteins)

They are produced during transcription of P gene by alternative mRNAs (Jordan et al., 2000). Incorporation of one guanine residue produces a V-gene, whereas incorporation of 2 guanine residues develops a W-gene. All the three phospho-gene-derived proteins share an amino terminus but diverge in sequence and their amino acid content at the carboxyl end. Their mRNAs expression differs in the infected cell. P-encoding mRNA was found in the highest level (68%) followed by V-encoding mRNA (29%) followed by W-encoding mRNA (2%).

The carboxyl-terminal region of V protein contains a high cysteine and binds to zn atom (Steward et al., 1995). Contrary to other paramyxoviruses, the V protein is found to be incorporated in virions (Park et al., 2003). It has been suggested that V protein could be one of the virulence determinants NDV (Huang et al., 2003). It could be acting as an IFN antagonist. This suggestion was supported by variation in the V protein amino acid sequence among NDV strains (Huang et al., 2003). Similarly, variation in sequences and length of W gene between AOAvV-1 strains has been reported, e.g., the length of W protein ORF in Ulster strain is 181 aa, in D26 is 141 aa, in Baudette C is 221 aa, and in AV is 228 amino-acid (Kawano et al., 1993). However, the W protein's function has not been established (Curran et al., 1991).

The virulence of NDV strains might differ depending on the functions and characteristics of NDV proteins. Unfortunately, the viral factors that determine AOAvV-1 pathogenicity are not totally identified. The sequence of amino acids at the location of F protein cleavage is a key factor in defining NDV virulence and typically separates virulent strains from avirulent ones (De Leeuw et al., 2005; Panda et al., 2004). Virulent NDV strains contain multiple basic residues and the cleavage motif (Arg-X-Arg/Lys-Arg2), which is ideal for the intracellular protease furin, that is found in all types of cells. In non-velogenic AOAvV-1 strains, which have limited basic residues and lack the furin motif, extracellular protease present in respiratory and gastrointestinal secretions cleaves the F protein at a single basic residue. Despite the fact that fusion gene sequence at cleavage site determines AOAvV-1 tropism and plays a significant role in AOAvV-1 pathogenesis, it is unclear how variation in the F protein sequence of cleavage motif affects the degree of virulence of different strains within the same pathotype (Estevez et al., 2007; Peeters et al., 1999). Since the pathogenicity of NDV strains with the same F protein cleavage sites might occasionally vary significantly. For instance, the velogenic GB Texas strain (GBT) and the mesogenic Beaudette C strains (BC) both have the same cleavage site (^{112}RRQKR2F^{117}). Additionally, the pathotype may not always be predicted from the cleavage site's structure (Tan et al., 2008), whereas others have velogenic motifs but do not appear to be virulent (de Almeida et al., 2009). The results above suggest that viral factors other than cleavage site amino acid sequences may be involved in the diversity in NDV strain pathogenicity. The haemagglutinin- neuraminidase genes, that comprises both the virus's receptor detection and NA activities, was investigated for its role in virulence (Estevez et al., 2007; Huang et al., 2004b). It has been discovered the HN gene determines virus replication site and has only a minor effect on virus virulence (Huang et al., 2004b). This conclusion was confirmed by replacing haemagglutinin-neuraminidase protein of a mesogenic AOAvV-1 strain with the HN gene of velogenic AOAvV-1 strains without increase in the virulence of the chimeric

viruses (Estevez et al., 2007). Furthermore, reverse genetic analyses of the two F and HN proteins revealed that the envelope genes, along with their homotypic connections, are not the key components of AOAvV-1 pathogenicity (Estevez et al., 2007). These findings imply that different virus proteins other than F and HN contribute to AOAvV-1 pathogenicity. Therefore, NDV virulence could be a multigenic feature as suggested by (Paldurai et al., 2014; Rout and Samal, 2008). Even while the other viral proteins often did not contribute much to virulence, they did have an impact on the virus's total virulence. For example, L protein enhances the overall pathogenicity of NDV. Additionally, it appears that the viral replication complex (NP, P, and L) is the most crucial element in the process of transcription. Dorman et al. demonstrated the importance of NP, P, and L in NDV virulence (Dortmans et al., 2010a). Additionally, by changing tryptophan in the site 123 of the HN genes into cysteine and cysteine in the site 27 of the F gene into arginine, the pathogenicity result of ICPI was raised to 1.5. Disulfide-linked HN dimers were produced as a result of the HN mutation, which may suggest that this HN conformation is beneficial to the virulent phenotype (Römer-Oberdörfer et al., 2006). HN has also been linked to NDV viral infectivity and virus-neutralizing antibody responses (Chambers et al., 1988; Cho et al., 2008; Connaris et al., 2002), e.g., HN point mutation at residues 347 could affect antigenicity and consequences of vaccination (Tran et al., 2020; Zhu et al., 2016). Based on these data, we may conclude that NDV virulence is multigenic, meaning that more than one protein can contribute to NDV virulence.

NDV epidemiology and its relation to virus contagiousness:

Host species

NDV could infect a wide range of avian species, about 250 domestic and wild bird species (Mayo, 2002). Although it may naturally or experimentally impact other species (humans, rodents). Non-avian animals may spread the disease, although the significance of this is unknown. These animals, however, pose a significant risk since they can act as mechanical vectors for NDV infection (Beard, 1984; White and Jordan, 1963). The virus's virulence differs across species. Poultry is the most prone to infection. Other commercial species, like as turkeys and ducks, are also susceptible to infection, although the clinical indications are less. Furthermore, virulent viruses have been found in backyard ducks with no signs, putting other types of fowl in danger (Wajid et al., 2016). NDV could also be zoonotic (Suarez et al., 2020).

1) Wild birds:

The first recorded NDV-related mortality event in wild bird types, young cormorants, discovered in 1975 in Canada (Wobeser et al., 1993). Cormorants work as a reservoir for AOAv- viruses. They have the ability to shed deadly ND virus for up to 6 weeks. Numerous deaths of wild birds have been reported in Canada. Wild migratory birds was involved in spread of epidemics in Europe (Kuiken, 1999). Canaries are also at risk for NDV infection, but with mild or inapparent disease. However, deaths of 20%-30% detected in experimental infections with significant neurologic symptoms (Erickson et al., 1977). Ratites can also get infection, but only young ages show clear clinical symptoms (Alexander et al., 2003a; Verwoerd, 2000). Psittacine are highly susceptible to NDV infection, budgerigars are more prone to NDV infection than canaries. The neurological signs are mainly observed during infection (Erickson et al., 1977). Tropical parrots serve as reservoir for velogenic strains and have been responsible for several

introductions to the United States. Infected psittacine can shed the virus for more than one year (Panigrahy et al., 1993; Roy et al., 1998).

Wild birds may serve as a reservoir for both low and high virulent strains of NDV posing an important role in the epidemiology of these viruses (Cappelle et al., 2015; Habib and Shabbir, 2018; Jørgensen et al., 2004). AOAvV-1 GVII is the most common one in fowl in the Middle East, with the majority of AOAvV-1 isolates from wild birds also belonging to this genotype (Kim et al., 2007a). A recent investigation carried out on the role wild bird species in transmission of AOAvV-1 in Egypt indicated detection of velogenic NDV-VII in cattle egrets and house sparrows (Abd Elfatah et al., 2021). Such data support the idea of avian pathogen interactions between wild birds and farmed chickens.

2) Domestic birds:

a) Chickens and turkeys

Chickens are the most susceptible of domestic poultry species to AOAvV-1 and the pigeon variant (Alexander et al., 2012). Turkeys are as susceptible as chickens to AOAvV-1; however, the infection is usually milder than that in chickens (Alexander et al., 2003b; Alexander et al., 1999; Box et al., 1970).

b) Waterfowls

Ducks attract infections by different Avian paramyxovirus serotypes as APMV1,4, 6, and 8 which were isolated from migratory and resident ducks in coastal Louisiana, USA (Stallknecht et al., 1991). In addition, (Lipkind et al., 1995)discovered a mixed population of viruses from Avian paramyxovirus serotypes 1 (APMV-1) and 2 (APMV-2). Long ago, waterfowls such as geese and ducks were considered as reservoirs for avirulent AOAvV-1 and resistant hosts to AOAvV-1 virulent strains (Alexander et al., 2003b; Huang et al., 2004a; Otim et al., 2006). However, continuous outbreaks of ND by genotype VII viruses have been noted in waterfowls since 1997 (Hualei et al., 2000; Jinding et al., 2005).

According to (Wu et al., 2015) both avirulent and virulent AOAvV-1 strains are circulating in domestic ducks, with at least four genotypes (class I and class II (I, II, IX, VII)). The genetic diversity of NDV strains obtained from ducks was established by (Liu et al., 2008). The principal pathogens are viruses of genotype VII virus, which have caused epidemic infections in ducks in China. Meanwhile, in other areas, rare infections were produced by an ancient lineage, such as viruses of the IX genotype (Liu et al., 2008). The AOAvV-1 GVIId from geese or hens may attack with production of infection in both species, with no host-associated genetic or phenotypic differences (Wang et al., 2012). Moreover, the apparently healthy ducks may be carriers of virulent AOAvV-1 strains causing a lot of deathes in chickens (Meng et al., 2018). Two sources of infection in ducks by AOAvV-1 including duck-origin AOAvV-1 and chicken-origin AOAvV-1 were reported (Meng et al., 2018). They have different effects on affected ducks, duck-origin AOAvV-1 strains cause lower mortality, whereas chicken-origin AOAvV-1 strains, which belong to the same genotype, cause higher tissue damage and mortality (Meng et al., 2018). Ducks may play an important role in driving AOAvV-1 evolution, and One of the routes of viral spread in backyard chickens is the carrier ducks (Zahid et al., 2020; Zhang et al., 2011). For example, the isolated strains by (Lipkind et al., 1995), were shown to be pathogenic to chickens despite being isolated from apparently healthy ducks. But (Lipkind et al., 1995) did not studied the change of sequence at the NDV fusion protein cleavage site after transmission to chicken. (de Leeuw et al.,

2003) demonstrated that changes of the sequence of fusion protein cleavage site occurred after passage in chicken brains. The most common and severe symptoms of NDV infection in ducks include decreased egg production, a problem with respiration, high death rates, and decreased body weight (OIE, 2012). The susceptibility of avian species to NDV varies, however, waterfowl such as ducks and geese are often resistant to velogenic NDV (Miller and Koch, 2013; Zhang et al., 2011).

This variation in NDV susceptibility is thought to be related to the innate immunity. Different cytokine production patterns in chicken peripheral blood and spleen have been linked to NDV infection with varying levels of virulence, according to earlier research (Hu et al., 2012; Liu et al., 2012; Rue et al., 2011). It's possible that altering cytokine responses contributed to the pathogenesis of this highly virulent strain in chickens (Hu et al., 2012; Liu et al., 2012; Rasoli et al., 2014; Rue et al., 2011). Despite this, no studies have looked at the host innate immunity in ducks infected with different pathogenic AOAvV-1 as a determinant for figuring out how an infection would progress. The RLRs (Retinoic acid-inducible gene-like receptors) detect RNA viruses with negative sense and function as sensors for viral infections, much like RIG-I (retinoic acid-inducible gene-I) and MDA5 (melanoma differentiation-associated gene 5) (Reikine et al., 2014). RLRs activate signaling pathways that support the production of IFN type I (alpha and beta). Chickens only express MDA5, but waterfowl like ducks and geese express both RLRs (Barber et al., 2010; Sun et al., 2013). It is known that the AOAV-1 V protein inhibits the synthesis of IFN and the signalling pathway by focusing on a variety of host factors, including MDA5 (Childs et al., 2007; Sun et al., 2019). As a result, RIG-I is expected to help ducks generate an efficient antiviral response (Kang et al., 2015; Rehman et al., 2018; Sun et al., 2013).

c) Pigeons, Quail, and Doves:

Pigeons and doves can be affected by NDV (Barton et al., 1992); however, pigeons are susceptible to pigeon-specific NDV(PPMV-1). The pigeon variant of APMV-1(AOAvV-1) can lead up to up 80% morbidity, with nervous signs and diarrhea being the most noticeable clinical signs (Dortmans et al., 2011c; Reham A. Elbhnsawy et al., 2017; Souza et al., 2018).

ND in pigeons is caused by pigeon paramyxovirus type 1 (PPMV-1), which is an antigenic and host variant of the avian paramyxovirus serotype 1 (APMV-1), as well as by other eleven bird paramyxovirus serotypes (APMV-2 to APMV-12) from the Paramyxoviridae family, subfamily Avulavirinae, and genera (Metaavulavirus, Orthoavulavirus, and Paraavulavirus) (Amarasinghe et al., 2019). PPMV-1 belongs to a unique subgroup (sub-genotype VIb) of Class II genotype VI. The F proteins of PPMV-1 is closely related to those of virulent strains (Wang et al., 2015). Although PPMV-1 is highly adapted to pigeons, it is nevertheless considered a threat to poultry (Olszewska-Tomczyk et al., 2018). It has spread to chickens in different countries, leading to several outbreaks (Alexander et al., 1985). Kommers et al. demonstrated that the infection by PPMV-1 isolates can cause depression and nervous indications in only part of the inoculated birds (Kommers et al., 2001). Moreover, some PPMV-1 strains were found to be highly pathogenic for chickens after serial passages in chickens (Dortmans et al., 2011a; Dortmans et al., 2011b). In addition to PPMV-1, the Columbidae family was revealed to harbour another avulavirus serotype. Alexander et al. isolated the Metaavulavirus genus's Avian avulavirus 7

(AAvV-7) from hunter-killed doves and identified it as a novel serotype (Alexander et al., 1981). AAvV-7 was also reported in ostriches and turkeys (Saif et al., 1997; Woolcock et al., 1996). Quail could be infected with PPMV-1 but with to less severe signs than pigeons (El-Bagoury et al., 2014).

Natural APMV-1 infection can kill game birds, and deaths have been reported. When it happens in quail, which are extremely vulnerable, infection normally results in only minor illness (Crespo et al., 1999). In general, clinical signs and lesions of APMV-1 infection of game birds showed patterns like those observed in chickens (Kinde et al., 2005).

Reservoir

Columbidae (pigeons and doves) and double-crested cormorants were documented as reservoir hosts of virulent NDV strains in North America (Cross et al., 2013). Wild ducks, gulls, and shorebirds could be reservoirs for non-virulent viruses (Ramey et al., 2017; Takakuwa et al., 1998). Overall, our data suggest that viral spread could arise between wild birds and chickens (Zhu et al., 2010), but majority of wild birds are likely not reservoirs for virulent strains with exception of pigeons, doves, and double-crested cormorants. Psittacine birds could be considered as reservoirs because they presented the virus to some poultry flocks in some outbreaks (OIE, 2021).

Transmission

ND is a fatal disease that spreads readily from bird to bird. NDV infection is often spread by direct contact with sick or unaffected birds harboring the virus; however, even vaccinated birds that are clinically healthy can shed virulent viruses after being exposed (Utterback and Schwartz, 1973). Direct contact transmission occurs mostly by food or gasp of discharges from infected birds' respiratory tracts, mouths, cloacas, or eyes (Manchang et al., 2004). The virus can also be spread indirectly by humans, other animals, machinery, cars, infected poultry products, feed, and water. AOAvV-1 can be transported through airborne particles from sick birds' coop or else infected area to a free region. It has been proved that the virus may be transmitted across sixty-four meters (Guittet et al., 1997).

Infected birds spread viruses by aerosol, respiratory discharge, and excrement. Virus excretion starts during incubation and can continue to convalescence (Utterback and Schwartz, 1973). Virus shedding can occur through faeces of infected. Infection can occur through ingestion of food contaminated with fecal matter; this is most likely the major mechanism of transmission for enteric non virulent AOAvV-1 and the pigeon variant virus (Alexander et al., 1984).

Vertical transmission is still debatable. The real relevance of such transmission in NDV infection epizootics is unknown, although it results in embryo mortality (McFerran and McCracken, 1988).

Infected chicks may hatch from contaminated eggs infected with non virulent viruses that do not always kill the embryo (French et al., 1967).

NDV infection and disease outcome:

NDV often enters the body through the intestinal and/or respiratory tracts. The virus quickly spreads to the blood stream after replicating at the site of introduction before being transported by the blood to other organs. The virus's virulence is primarily responsible for how quickly it spreads. Mesogenic strains spread to the kidney, lungs, bursa, and spleen, whereas lentogenic strains are only present in the circulation at low titers. Nearly all tissues can contain virulent NDV within 22–44 hours, with the thymus having the greatest titers and the muscles and brain having the lowest titers. The virus is discharged into the blood

stream during second replication, which also results in a rise in viral titer. This is linked to the emergence of general illness symptoms as well as viral excretion into the environment via faeces and respiratory secretions. The central nervous system, as well as the respiratory and digestive tracts, are infected at the same time by virulent neurotropic NDV. Viruses move across the blood-brain barrier at a rapid rate, causing serious damage to the barrier.

Depending on type of AOAvV-1 strains and the species of bird, the clinical symptoms of NDV infection might change. Generally, viscerotropic velogenic NDV strains cause severe depression and greenish or white diarrhea and are associated with high mortality rates. In addition to respiratory difficulties. Neurotropic velogenic NDV strains induce neurological symptoms including ataxia, head tremors, and paresis. Mesogenic NDV strains have been linked to respiratory disease and mortality in young birds. Lentogenic strains seldom induce clinical symptoms, but when they do, they are often respiratory in nature. Non- virulent NDV strains usually not cause any clinical signs at all. However, several pathotypes overlap, and age, immunological status, and the presence of concurrent diseases should all be taken into account when evaluating clinical symptoms (OIE, 2012).

Histopathology of NDV infection in different forms of the disease:

The pathotype of AOAvV-1 affects the macroscopic and histological characteristics of NDV infection. The central nervous system and lymphoid tissue are both prominent velogenic viral tropism (Cattoli et al., 2011).

Infection with viscerotropic velogenic (vVNDV) pathotypes is characterized by multifocal hemorrhages on the serosal surface of the intestines, multifocal areas of necrosis and/or ulceration of the gut-associated lymphoid tissue (GALT), and disseminated foci of necrosis in the spleen (Alexander et al., 2003b; Alexander, 2001; Brown et al., 1999b; Kommers et al., 2003a). The cecal tonsils frequently exhibit gross hemorrhage and necrosis which are characteristic lesions for vNDV. The proventriculus-gizzard interface displays multifocal hemorrhages and ulceration which are additional frequent intestinal lesions. In the most severe instances, the spleens are enlarged and extensively mottled, with many neccrotic foci (Kommers et al., 2003a; Susta et al., 2011). Periodically, hemorrhages are seen around thymus, and with the advance of the disease, the thymus and bursa become severely atrophy (Kommers et al., 2002b; Susta et al., 2011).

Infection with neurotropic velogenic (nVNDV) strains causes modest lesions on the serosal surface of the intestines, but it can cause respiratory illness with hemorrhagic tracheitis and increased exudate in the bronchioles and trachea. Despite their neurotropism, these strains do not exhibit macroscopic lesions in the central nervous system. In contrast to vVNDV infection, nVNDV infection has no distinguishing gross lesions. In reality, in the vast majority of instances, gross lesions are absolutely absent (Alexander et al., 2003b; Brown et al., 1999b).

Mesogenic viruses exhibit very little gross pathogenic alterations in the laboratory, with the exception of splenic enlargement and increased air sac opacity (Brown et al., 1999b). Lentogenic strains provide very minor gross observations.

In general, viscerotropic velogenic NDV strains cause severe lymphoid, digestive, and respiratory tract lesions. AOAvV-1 tropism mostly depends on the viral pathotype. However, diverse virulent NDV strains with high virulence that share a common F cleavage site cause varied clinical manifestations in chickens,

particularly in lymphoid organs (Merino et al., 2011; Susta et al., 2011; Wang et al., 2012).

According to certain recent research, Some NDV GVIId isolates produce more lymphatic organ tissue destruction than other velogenic strains of NDV (Hu et al., 2015; Susta et al., 2011; Wang et al., 2012). In addition, both in-vitro and in-vivo investigations showed that high levels of viral replication, as well as a considerable inflammatory response, contribute to this clinical manifestation of NDV GVIId (Hu et al., 2012; Hu et al., 2015).

According to (Kai et al., 2015) , the envelope genes of AOAvV-1 GVIId are the cause of significant degenerative changes in the spleen. AOAvV-1 GVIId increases viral replication and cytokine gene production in the spleen, resulting in extensive necrosis and significant lymphocyte depletion.

Furthermore, the envelope genes mediate the replication site of pathogenic AOAvV-1-GVII to macrophages (Cornax et al., 2013). One of the most significant feature of AOAvV-1-GVII infection that it could inhibit autophagy-regulated cell death (Rabiei et al., 2021), which may be related to the highest levels of NP and P gene expression. Apoptosis is a defining feature of AOAvV-1infected cells that can activate both extrinsic and intrinsic apoptotic pathways (Lam and Vasconcelos, 1994; Ravindra et al., 2008). Cell death of lymphatic tissue and other immune cells by AOAvV-1-GVII infection has been confirmed by several studies (Brown et al., 1999a; Kommers et al., 2003a). This mechanism of AOAvV-1-GVII infection leads to severe splenic disruption, enormous lymphoid depletion, intestinal epithelium ulceration, and rapid depletion of the cells of bursa of Fabricius (Kommers et al., 2002a; Kommers et al., 2001).

Although ND is normally asymptomatic in wild birds, double-crested cormorant outbreaks had nervous signs manifestation (Glaser et al., 1999). Cormorants' primary clinical symptom was an inability to fly, frequently accompanied by unilateral wing or limb paralysis. The brain and spinal cord had just a few macroscopic lesions, but histological investigation indicated gliosis, white matter vacuolation, and mononuclear perivascular cuffing (Glaser et al., 1999; Meteyer et al., 1997).

Host response to NDV infection:

The respiratory tract is the major entry site for AOAvV-1. Therefore, local immune response acts as the primary line of defense against AOAvV-1infection. In contrast to mammals, chicken respiratory lavage fluids contain a low amount of avian respiratory phagocytes (macrophages and heterophiles). Birds appear to compensate for the scarcity by quickly influxing respiratory phagocytes against invading pathogens. The inflow of leukocytes in the respiratory tract lumen has not been studied in the case of ND, although some reports suggested that AOAvV-1infection may have adverse impact on these cells. Moreover, avian pulmonary phagocytes in AOAvV-1vaccinated birds displayed low functional activity, which might be one of the reasons for post vaccinal bacterial infection reactions, e.g., Mycoplasma (Toth, 2000). NDV targets the respiratory lining epithelium first, then the gastrointestinal system, depending on the viral type (Cheville et al., 1972). Despite the fact that the culture media from infected fibroblasts have shown antiviral activity and no production of chicken macrophages, NDV leads to the induction of interferon type I and type II in fibroblasts in vitro (Heller et al., 1997).

The AOAvV-1 infection enhance nitric oxide and interferons (alpha, beta and gamma) during the course of infection (Susta et al., 2013). IFN- is an interferon of type I that may be generated by most cells upon viral

infection. It helps to localize viral infections by inhibiting virus multiplication (Martínez-Sobrido et al., 2006). IFN alpha levels in host cells peaked three days following NDV infection. At that moment, innate immunity mediated by IFN- α is more significant than specific immunity. However, when IFN-α levels dropped sharply, it is possible that adaptive immunity was begun, and innate immunity continued its function till the late stages of the disease. The over stimulation of the non-specific immune response might enhance apoptosis, which would aggravate AOAvV-1 pathogenesis.

IFNs have a crucial role as apoptotic mediators. The 2',5-oligoadenylate/RNase L system, IFN regulatory factor, and protein kinase R are all different ways that the IFN pathway's components affect apoptosis (Barber, 2001). IFNs can also trigger TRAIL (TNF- related apoptosis-inducing ligand), which accelerates cell death by activating the death receptor (Barber, 2001).

As antibody and cellular T-cell responses are common in viral infections, when NDV overcomes the innate response, it is prone to trigger both an antibody and a cellular T-cell response (Zinkernagel, 1994). The F and HN antigens are necessary for a protective avian immune response to NDV (Seal et al., 2000b).

In viral replication sites such as the respiratory tract and the Harderian gland (HG), leukocyte infiltrates do grow over time (Russell et al., 1997). All of the components required for the initiation of a cellular immune response are present in leucocyte infiltrates, including macrophages and CD4 and CD8 T cells (Al-Garib et al., 2003; Russell et al., 1997). Because many of the infiltrating leukocytes exhibit MHC class II epitopes, the majority of infiltrating lymphocytes in the tracheal mucosa and HG express TCR1. T and B lymphocytes are already present in the HG of normal chickens, but after immunization with lentogenic or mesogenic viral strains, their numbers increased 2-3 times (Al-Garib et al., 2003; Russell et al., 1997). T CD8 cells get activated by phagocytosis by phagocytic cells, resulting in generation of cytokines that can either kill the target cells or utilize cells as macrophages to assault the cell of choice (Al-Garib et al., 2003). In contrast, T CD4 cell activation promotes B cells to proliferate and specialize in antibody production, as well as the generation of memory B cells (Ramakrishnan et al., 2015). Antibodies are vital in viral defense since they eradicate and neutralize pathogens in two ways: 1) by attaching to the infected cell, inhibiting virus production; and 2) by linking to the progeny virus, preventing virus transmission (van Boven et al., 2008). Many classes of antibodies have been produced during AOAvV-1 infection with higher levels of IgM and IgG (Zhao et al., 2016). IgM levels peak in the first 4 days, followed by IgA and IgG rises. Virus replication in the respiratory mucosa is inhibited by serum antibodies, but virus replication in the epithelium is inhibited by secreted antibodies (Al-Garib et al., 2003). Several studies have demonstrated the protective advantages of NDV viral antibodies. The presence of antibodies is shown by HI and NT assays, and their role in protecting the host against the virus is investigated (Samuel et al., 2013). In general, humoral immunity plays a significant role in the host's defense against viral pathogens (Reynolds & Maraqa 2000b). The virus boosts antibody titer when inactive antibodies are created prior to AOAvV-1 infection within 4 days of persistence in the trachea (Kapczynski and King, 2005). Antibodies against the virus's F and HN glycoproteins protect the host from the virus in terms of NDV antibody performance (Reynolds and Maraqa, 2000). Simultaneously, certain non-conserved

residues on viral mRNA may be effective on viral glycoprotein alterations recorded by neutralizing antibodies. As a result, this might be a good way for the virus to avoid neutralizing antibodies from the host (Palya et al., 2014). Hu et al. (2012) found that GVIId AOAvV-1 isolates generated higher innate immunity and apoptosis in splenocytes of chicken than GIX and GIV AOAvV-1strains (Hu et al., 2012). This implies that dysregulation of the host response may play a role in the significant tissue damage induced by genotype VIId AOAvV-1 in the lymphoid system.

Determination of NDV Pathogenicity:

The virulence differences between AOAvV-1 strains are studied using chicken and chicken embryo inoculation. To make such differentiation, four pathotyping tests are employed; (intracerebral pathogenicity index in one-day-old chicks from specific-pathogen-free (SPF) parents, intravenous pathogenicity index in six weeks-old SPF chickens, intra-cloacal inoculation pathogenicity test in 6–8-week-old chickens, and mean death time in 9-10-days-old embryonating eggs). In accordance to Clinical manifestations and death in hens, as well as the duration of embryo death following inoculation, viruses are classed as having low (lentogenic), moderate (mesogenic), or high (velogenic) virulence(Alexander et al., 2003a; Pearson JE, ,1975).

The interaction between cellular proteases and cleavage motif of fusion gene is considered one of the main determinants of AOAvV-1 pathogenicity. An isolate will be considered virulent if it has an ICPI of 0.7 or higher or a dibasic amino-acid the F protein cleave site (OIE, ,1999). several species of poultry are at risk for AOAvV-1, and the disease and deaths rates of ND change significantly according to the pathogenicity AOAvV-1 strains, the viral tropism for the bodily systems, and the avian species afflicted. Previous study has shown that isolates from non-avian species can lack their virulence for domestic chickens until they have been transmitted through chickens several times (Alexander et al., 2003a).

Merino et al. (2011) investigated the pathogenicity of AOAvV-1 utilizing the lesion score for bone marrow and the Harderian gland (Merino et al., 2011). Susta et al. (2011) proved that viruses of the same genotype may have differential virulence and that viruses of different genotypes can have variable virulence. As a result, animal trials are useful for investigating the variation in AOAvV-1 pathogenicity (Susta et al., 2011). As a result, experiments on animals are helpful to investigate the variance in AOAvV-1 pathogenicity. All of these data indicate that not the ICPI nor the F protein cleavage site is adequate to predictors virulent viral clinicopathological outcomes (Wakamatsu et al., 2007).

CONCLUSION

Although the use of different vaccination programs and technologies for control of NDV, virus is still a threatening agent for poultry industry. The emergence of NDV GVII complicated the process of control of NDV. From this review, we proposed understanding the transmission cycle of NDV from wild birds to waterfowl and from waterfowls to domestic birds (particularly ducks) should be thoroughly investigated in depth. Therefore, the effect of this transmission on virus evolution and alteration in virus virulence should be a target for research. The mechanism of change in molecular pathogenicity of NDV strains should be also resolved. Based on the current knowledge of NDV, the contact between different poultry species in the backyard system in Egypt should be prohibited.

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