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Avian adenovirus infections: diversity of pathogens, hazard to poultry industry and problems of immunoprophylaxis (review)

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ABSTRACT

The data on diversity of adenovirus pathogens in nature and the role of the main representatives of the *Adenoviridae* family in poultry infectious pathology are presented. Special attention is paid to problematic issues of immunoprophylaxis due to lack of cross-immunity between different virus serotypes. There is no single and effective approach in the global strategy of immunoprophylaxis of avian adenoviruses, therefore, improving the means of avian adenovirus disease control is an urgent and important task. Avian adenovirus infections are represented by different nosological units: egg drop syndrome, hydropericardium syndrome, adenoviral gizzard erosion, marbled spleen disease of pheasants, hemorrhagic enteritis of turkeys, inclusion body hepatitis and many unclassified diseases. The paper provides data on the main nosological forms of adenovirus infections that pose a threat to cost-effective poultry farming, and highlights test results obtained by foreign authors on the effectiveness of some vaccines against adenovirus infection. Most vaccines have been developed to prevent avian hydropericardium syndrome, however, occurrence of many virus serotypes requires effective means of prevention and diagnosis in order to control other infections caused by adenoviruses. There is no registered vaccine against adenovirus infections that cause inclusion body hepatitis and adenoviral gizzard erosion. At the same time, inclusion body hepatitis alone accounts for 2.9% of all recorded avian infectious diseases. Vaccines registered in the Russian Federation are not enough to fully control these infections, and that requires a timely solution to the problem. The variety of avian adenoviruses determines the problems of their differential diagnosis and specific prevention.

Keywords: review, avian adenovirus infections, *Aviadenovirus*, *Atadenovirus*, *Siadenovirus*

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Аденовирусные инфекции птиц: многообразие возбудителей, опасность для птицеводства и проблемы иммунопрофилактики (обзор)

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РЕЗЮМЕ

Представлены данные о многообразии возбудителей аденовирусных инфекций в природе и роли основных патогенов семейства *Adenoviridae* в инфекционной патологии сельскохозяйственной птицы. Особое внимание уделено проблемным вопросам иммунопрофилактики ввиду отсутствия перекрестного иммунитета между разными серотипами вируса. В мире нет единого и эффективного подхода в стратегии иммунопрофилактики аденовирозов птиц, поэтому совершенствование средств борьбы с аденовирусными заболеваниями птиц является актуальной и важной задачей. Аденовирусные инфекции птиц представлены разными нозологическими единицами: синдромом снижения яйценоскости, синдромом гидроперикардита кур, эрозией желудка, болезнью мраморной селезенки фазанов, геморрагическим энтеритом индеек, гепатитом с тельцами-включениями и множеством неклассифицированных болезней. Приводится информация об основных нозологических формах аденовирусных инфекций, представляющих угрозу

для рентабельного ведения птицеводства, освещены результаты исследований зарубежных авторов по изучению эффективности некоторых вакцин против аденовирозов. Большинство вакцин разработаны для профилактики синдрома гидроперикардита кур, однако существование множества серотипов возбудителя требует создания эффективных средств профилактики и диагностики в целях контроля и других инфекций, вызываемых аденовирусами. Нет ни одной зарегистрированной вакцины против аденовирусных инфекций, вызывающих гепатит с тельцами-включениями и эрозию желудка. При этом на долю только гепатита с тельцами-включениями приходится 2,9% от всех регистрируемых инфекционных заболеваний птиц. Вакцин, зарегистрированных на территории Российской Федерации, недостаточно для полного контроля данных инфекций, что требует своевременного решения проблемы. Многообразие возбудителей аденовирусных инфекций птиц обусловливает проблематику их дифференциальной диагностики и специфической профилактики.

Ключевые слова: обзор, аденовирусные инфекции птиц, *Aviadenovirus*, *Atadenovirus*, *Siadenovirus*

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INTRODUCTION

Food security is a global problem, and poultry farming accounting for about 39% of the global meat production plays a leading role in solving it. In Russia poultry meat accounts for 46% of the total meat production [1]. It should be noted that confessional restrictions do not apply to poultry products – no religion prohibits consumption of chicken meat or eggs [2].

Poultry industry is greatly affected by infectious diseases, not only highly dangerous, but also economically significant, such as adenovirus infections tending to spread widely. Previously researchers did not pay much attention to fowl adenoviruses (FAdV) due to their limited clinical significance, but in recent decades adenoviruses became significant field pathogens causing diseases that have a serious impact on poultry health and industry profitability. In this regard the number of FAdV scientific studies began to grow [3, 4]. In recent years, new data on cross-immunity between different serotypes of adenoviruses were obtained, inactivated, live and recombinant vaccines against certain diseases of adenovirus etiology were developed, and their immunogenic activity was studied.

The aim of this work was to summarize scattered information on fowl adenoviruses with special emphasis on the diversity of pathogens and the problem of effective immunoprophylaxis, as well as to show the role of some adenovirus diseases in avian infectious pathology.

ADENOVIRUSES: TAXONOMY, DESCRIPTION, SUSCEPTIBLE ANIMALS

Adenoviridae is a family of non-enveloped viruses with icosahedral symmetry, 90 nm in diameter. Nucleic acid is represented by double-stranded linear DNA (25–48 kilobase pairs) with inverted terminal repeats and a terminal TP protein (55 kDa) covalently bound to each 5'-end of both chains [5, 6, 7, 8]. The viral capsid has a pseudo-triangulation number of 25 and consists of 252 capsomers: 240 hexones and 12 pentones with fibrous processes ranging in length from 9.0 to 77.5 nm [5, 9].

Adenoviruses were found in many vertebrates from fish to humans and are represented by six genera:

– *Mastadenovirus*: 51 species with a capacity to infect mammals, including humans;

– *Aviadenovirus*: 16 species infecting birds;

– *Atadenovirus*: 10 species with a capacity to infect reptiles, birds, ruminants and marsupial mammals;

– *Siadenovirus*: 8 species infecting frogs and birds;

– *Ichtadenovirus*: 1 species infecting belugas;

– *Testadenovirus*: 1 species infecting red-eared sliders.

The demarcation of the genus is based on phylogenetic, biological characteristics, as well as on the organization of the genome [5, 10, 11].

Birds are affected by representatives of three genera of the family *Adenoviridae*:

– *Aviadenovirus* (FAdV) includes species A, B, C, D, E divided into 12 serotypes using a cross-neutralization test that cause inclusion body hepatitis, hydropericardium syndrome and gizzard erosion in both domestic and synanthropic birds;

– *Siadenovirus* causes hemorrhagic enteritis in turkeys, marble spleen disease in pheasants, adenovirus splenomegaly in chickens;

– *Atadenovirus* is a duck adenovirus that is pathogenic to chickens and causes egg drop syndrome (EDS–76) [5, 12].

Thus, the variety of avian adenovirus infectious agents determines the problematic issues of their differential diagnosis and specific prevention.

MAIN AVIAN ADENOVIRUSES

Egg drop syndrome (EDS-76) is a fowl adenovirus infection affecting layers; it is manifested by decreased egg production, shell thinning (up to its complete loss) and depigmentation. It was first described by

Dutch scientists in 1976 [13]. The causative agent of EDS-76 is duck adenovirus (DAdV-1), contamination of the live vaccine against Marek's disease resulted in primary infection of chickens and adaptation to a new host [14]. The major characteristic of EDS-76 is decreased egg production by 15% or more [15]. Viral carriage is typical of this disease: in the vast majority of cases birds look healthy, the disease is not apparent but develops when a bird reaches reproductive maturity and experiences stress due to egg lay onset. EDS-76 is currently widespread in many countries with developed poultry industry [13].

Hemorrhagic enteritis of turkeys (HE) is a viral disease of poultry caused by adenoviruses belonging to the genus *Siadenovirus*, the species *Turkey siadenovirus A* (TadV-A), and manifested as immunosuppression in turkeys older than 4 weeks of age [16]. The disease has two forms. The first variant implies that hemorrhagic enteritis is caused by highly virulent strains of the pathogen and proceeds with pronounced clinical signs such as depression and gastro-intestinal hemorrhages. The virus causes immunosuppression, so opportunistic bacterial infections are often an intercurrent problem. This disease often results in poultry mortality (up to 80%) due to blood loss and secondary infection [17, 18]. The second form implies that hemorrhagic enteritis develops without visible symptoms and is caused by low-virulent strains of the virus that determine immunosuppression resulting in the development of secondary bacterial complications. This leads to economic losses due to necessity to use antibacterial drugs and perform culling [19, 20]. The disease is widespread in turkey populations all over the world [21].

Marble spleen disease of pheasants (MSD) is an infectious disease affecting 3–8 month-old pheasants which is caused by group II adenovirus of the genus *Siadenovirus*. The pathogen is closely related to the two other representatives of the genus: the causative agent of adenovirus splenomegaly in chickens and the causative agent of hemorrhagic enteritis in turkeys [22]. Typical signs of the disease observed during necropsy include splenomegaly and a marble spleen pattern. Congestion and pulmonary edema are detected. Necrotized lymphoid follicles and focal necroses in the liver are observed. The disease is clinically manifested as respiratory failure, asphyxia and sudden death. The mortality rate can vary from 1–3 to 15% [23], the disease is highly contagious and occurs all over the world [24].

Avian adenovirus splenomegaly (AAC) is a viral disease of chickens which is clinically, pathologically and anatomically similar to the marble spleen disease of pheasants. Necropsy performed in chickens reveals enlarged "marble" liver, degenerative changes in the lymphoid lung tissue, less frequently - pulmonary hemorrhages and pulmonary edema [25].

Adenoviral gizzard erosion (AGE) is a chicken disease caused by group I adenovirus FAdV-1. The capacity of avian adenoviruses to independently cause avian diseases has been disputed for a long time, but the leading role of FAdV-1 in the etiology of adenovirus gizzard erosion was proven in the last decade [26]. FAdV-1 belongs to the genus *Aviadenovirus*, species A (group I avian adenoviruses) [5]. The disease is widespread in Europe and Asia (Iran [27], Japan [28], Sweden [29], Korea [30]). The disease is clinically manifested by depression, anorexia [28], a decrease in weight gain and leads to death. The infection often proceeds without visible clinical signs and is diagnosed post-mortem only. Autopsy shows necroses and inflammation of the gizzard mucosa, and hemorrhagic fluid in the gizzard cavity is observed [26]. The disease spreads both vertically and horizontally (mainly via fecal-oral route) and affects both broilers and layers causing significant economic losses. Thus, during the outbreak of adenovirus gizzard erosion on a farm in Mazandaran province (Iran) in 2019, the mortality rate of broiler chickens was 6%, and the target slaughter weight was gained with a week's delay; besides, lots of affected gizzards were condemned at the slaughterhouse [27].

Avian hydropericardium syndrome (HPS) is a viral disease of poultry caused by fowl adenovirus FAdV-4 group I and leading to large economic losses in poultry industry. It generally affects 3–5 week-old broiler chickens. The mortality rate ranges from 30 to 80% in broilers and from 2.6 to 15.29% in pullets [31]. It was not possible to determine the cause of this disease for a long time. Its occurrence was associated with incompliances in poultry feeding and keeping schemes, mineral and vitamin imbalance, and toxicoinfection [32]. But this association was not further confirmed [33]. The detection of body inclusions in hepatocytes during histological studies gave reason to believe that HPS is caused by the virus [34]. Subsequently, the pathogen was isolated from the liver of chickens that died from HPS and was identified as a group I avian adenovirus [35]. The HPS pathogen is transmitted both vertically from vectors and infected birds, and horizontally through litter, feed, water and inventory contaminated with feces and excretions of infected birds [36, 37]. The hydropericardium syndrome virus is assumed to spread through live vaccines made using adenovirus-infected chicken embryonated eggs. Such cases were described in Pakistan [38]. The disease is often asymptomatic and is associated with sudden death. Diseased birds may demonstrate ruffled feathers, droopy wings, depression, dyspnea, loss of appetite, diarrhea with green to yellow droppings [39]. The disease manifestations depend on a large number of factors and their combination: feeding and keeping conditions, natural resistance of the body, genetics, presence of concomitant diseases. HPS is more often manifested in poultry in a state of immunosuppression due to such factor as infectious bursal disease, feed toxicosis. Pure breed poultry is found to get diseased less often than cross-breds in broiler industry [40]. Postmortem examination of diseased chicks reveals the following pathological and anatomical findings: an enlarged fiable liver with thickened edges of pale brown or yellowish color, sometimes with focal necroses; an overflowing gallbladder with strained walls; swollen kidneys; a deformed flabby heart, often with spot hemorrhages. The pericardial cavity is filled with a clear straw-yellow fluid with a viscous consistency (up to 20 mL) [41]. Anemia, swelling of subcutaneous adipose tissue, jaundice, hemorrhages in organs and

tissues may be observed [42]. Histological studies reveal basophilic and eosinophilic inclusion bodies in hepatocytes [43, 44].

Inclusion body hepatitis (IBH) is an acute viral disease of 2–7 week-old broilers, accompanied by stunting and sudden death, with mortality ranging from 10 to 30%. The inclusion body hepatitis was initially viewed as a secondary disease associated with immunosuppression, but later it was proved that the disease was infectious in nature, the causative agent was the avian adenovirus of group I – FAdV species D (serotypes 2, 11) and E (serotypes 8a, 8b), affecting both layers and broilers. Broilers are most susceptible to the disease, mainly young birds older than 2 weeks get diseased [45, 46, 47, 48]. Thus, 92% of all cases of inclusion body hepatitis were associated with broiler chickens in 2011–2021 in Spain. The pathogen mainly spreads horizontally, but a vertical transmission pathway is also noted [47]. The virus tends to reactivate with the onset of egg production, causing a subclinical course of the disease, providing vertical transmission [45]. Group I adenoviruses are capable of infecting not only chickens, but also other bird species [48], in particular, pigeons, ducks, quails, ostriches [47]. Clinical signs are non-specific, usually observed within 4–5 days and include depression, ruffled feathers, sedentary behavior, birds' maintaining a sitting position. Necropsy reveals extensive or focal necrosis in the liver that increases in size, has a fiable consistency and a pale color [45]. There are cases of pancreatic lesions involving necrosis and atrophy, as well as lesions in kidneys [46] and spleen [49]. Histological examination reveals lymphoid infiltration, focal necroses, cell degeneration [46] and basophilic intranuclear inclusion bodies in hepatocytes [45, 50].

Thus, fowl adenoviruses cause various diseases leading to serious economic losses [49], which are expressed in high mortality (up to 80% for HPS), reduced productivity and the need for forced antibiotic therapy against secondary bacterial infections occurring in the setting of adenovirus immunosuppression. This problem is relevant and urgent for poultry industry due to the abilities of adenoviruses to persist for a long time, reactivate, infect not only livestock, but also synanthropic and wild birds, as well as to spread with their help, to cause infection without visible clinical manifestations, to spillover (EDS-76 virus). Therefore, the development of methods for control of fowl adenovirus infections is an important task and should include not only the improvement of biosafety systems in commercial establishments, but also the development of surveillance programs, as well as specific immunoprophylaxis.

IMMUNOPROPHYLAXIS

Prophylactic immunization against adenovirus infections is of great importance and serves as an effective tool in disease control. A decrease in the body's defenses, immunosuppression and stresses caused by both man-made and biological factors are the reason for sudden manifestation of FAdV-induced diseases [51]. And taking into account the intensification of poultry production [13], control of adenovirus infections is becoming an increasingly urgent problem [26]. Several types of vaccines are used for immunization: subunit, live, autogenic, inactivated. Mainly inactivated vaccines have been developed and used for the prevention of FadV; organ-tissue formolized liver homogenate vaccines are most commonly administered. These vaccines demonstrated high immunogenicity in the field trials. Thus, according to study results, the protectivity level in vaccinated poultry challenged with a field homologous virus isolate ranged within 80.0–98.9%, while the incidence level in unvaccinated birds in the control group was 60–100%. Despite inducing high immunogenicity levels, these vaccines have some disadvantages, such as high cost and impossibility to standardize the antigen dose. A number of inactivated culture virus-based vaccines have been developed. Live vaccines based on attenuated adenovirus are also known around the world. The great advantage of such biologicals over inactivated vaccines is that they can be administered orally. In the field trials these vaccines conferred 94.7–100.0% protection against challenge with homologous virus in the setting of 30.0–100.0% incidence in unvaccinated birds. Trials of subunit vaccines based on recombinant proteins F1, F2, etc. have been conducted in recent years, but the disadvantage of such vaccines is their low immunogenicity [26].

The number of reports on evidence of cross-protection between serotypes belonging not only to one but to different species is increasing, although previously it was believed that group I avian adenoviruses lack or demonstrate weak cross-protection between serotypes [52]. However, this statement is controversial, since some researchers have proven the existence of interspecies cross-protection [45]. A number of studies revealed that vaccination of poultry with combined (FAdV-8a and FAdV-11) inactivated [53] or live [45] vaccines confers cross-protection not only against FAdV-8a and FAdV-11, but also against other serotypes of D and E species [52]. The results of another experiment showed that vaccination against FAdV-4 induced protection not only against the homologous serotype, but also against the FAdV-10 serotype, which, like FAdV-4, is a representative of C species [54]. A study conducted by P. A. Steer-Cope et al. in 2019 demonstrated evidence of interspecies cross-protection between D and E species [52]. It follows from the above that multi-strain vaccines are the most prospective and can protect birds from a wide range of pathogen strains.

Three vaccines against avian adenovirus infections induced by group I adenoviruses have been registered in Russia: inactivated adsorbed vaccine against avian hydropericardium syndrome (ARRIAH, Russia) [55], liquid inactivated vaccine against adenovirus inclusion body hepatitis – avian hydropericardium syndrome based on "T-12" strain (VNIVIP, Russia) and inactivated emulsion vaccine against adenovirus body inclusion hepatitis (AVIVAC) [56]. Unfortunately, there is no registered vaccine against FAdV-induced inclusion body hepatitis and gizzard erosion. At the same time, inclusion body hepatitis alone accounts for 2.9% of all recorded avian infectious diseases [56]. There are several vaccines available in our country to protect poultry from group III adenovirus causing egg drop syndrome: vaccine against EDS-76

based on strain "B8/78" produced by VNIVIP, inactivated mono- and polyvalent vaccines against EDS-76 (strains "BISS" and "B8/78") produced by Federal Centre for Animal Health and some other manufacturers [57].

Unfortunately, there is no single and effective approach in the strategy of preventive immunization against avian adenoviruses in the world, therefore, improving the means of combating avian adenovirus diseases is an urgent and important task [13].

CONCLUSION

Avian adenovirus infections are spread globally, including Russia, and pose a danger to economically effective poultry industry. Diversity of virus serotypes and isolation of individual nosological forms of adenovirosis cause significant challenges in the diagnosis and specific prevention of these infections. Given the absence or insufficiency of cross-protection between different adenovirus serotypes, an urgent problem is the development of specific preventive measures against each serotype of the causative agent of adenoviruses, causing a clinically significant infection. The variability of the adenovirus tropism, the ability to long-term persistence, recorded cases of spillover, a high incidence rate in some nosological forms (HPS, hemorrhagic enteritis of turkeys) require the development of infection control programs in commercial poultry industry, including active and passive monitoring of the pathogen's circulation.

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