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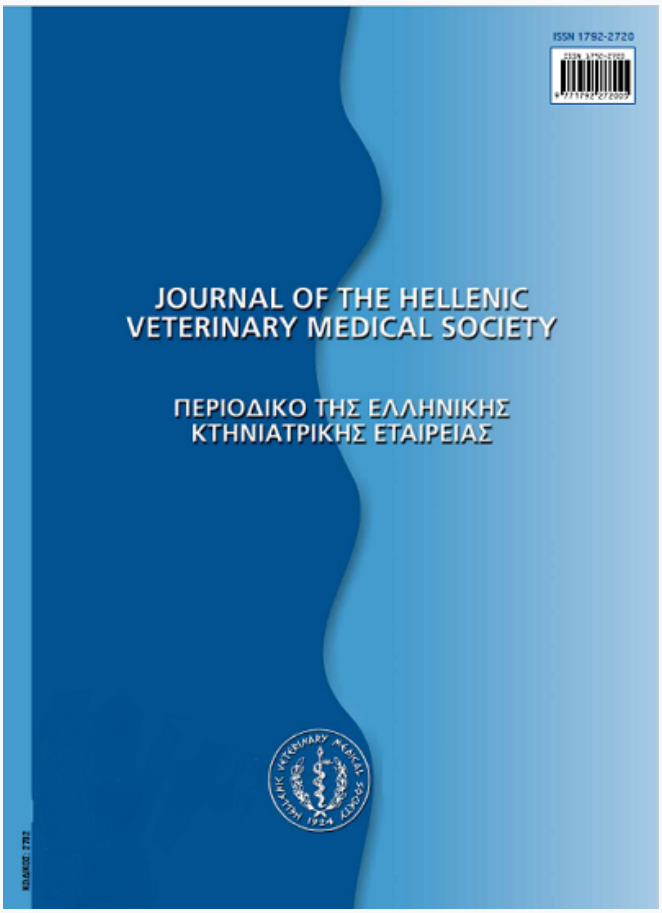

Aujeszky's Disease (Pseudorabies). An old threat in current pig industry? Part II. Epidemiology, Immunity, Prevention and the current situation in Greece

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Review article
Ανασκόπηση

Aujeszky's Disease (Pseudorabies). An old threat in current pig industry? Part II. Epidemiology, Immunity, Prevention and the current situation in Greece.

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Νόσος του Aujeszky (Ψευδολύσσα). Μια παλιά απειλή για τη σύγχρονη χοιροτροφία; Μέρος ΙΙ. Επιδημιολογία, ανοσία, πρόληψη και η τρέχουσα κατάσταση στην Ελλάδα.

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ABSTRACT. Aujeszky's disease (AD) (or pseudorabies) is an important viral disease of swine causing neurological signs in neonatal pigs, respiratory problems in fatteners and reproductive disorders in breeding stock. Swine is the only natural host of Aujeszky's disease virus (ADV) and the only species that can survive its infection. Its transmission is mainly through nose-to-nose contact, but several other ways may apply. Both antibody- and cell-mediated immune responses occur following ADV infection, while maternal immunity can protect the pigs depending on their level and the virulence of the infecting strain. Virus glycoproteins may, also, play a role in immunity with that of gC and gD being the most important. Prevention and control of ADV is based on proper vaccination and biosecurity measures, while eradication has been practiced in various ways depending on the situation. The current vaccines are based on deletion of certain proteins and are effective. Despite the fact that the disease has been eradicated

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from many developed countries, AD is still endemic in Greece. Findings of recent emergence of AD in Greek farms and the possibility of its eradication are discussed.

Keywords: Aujeszky's Disease, epidemiology, immunity, control, vaccination

ΠΕΡΙΛΗΨΗ. Η νόσος του Aujeszky είναι μια σοβαρή ιογενής νόσος του χοίρου η οποία για πρώτη φορά περιγράφηκε το 1813 στα βοοειδή. Η νόσος του Aujeszky παρουσιάζει παγκόσμια εξάπλωση, αν και έχει εκριζωθεί από αρκετές αναπτυγμένες χώρες όπως είναι η Γερμανία, η Αυστρία, η Σουηδία, η Ολλανδία, η Δανία, το Βέλγιο και το Ηνωμένο Βασίλειο. Στην Ελλάδα, η νόσος εμφανίζεται ενδημική και παρά το γεγονός ότι ο ιός δεν προκαλεί σοβαρά προβλήματα στις κτηνοτροφικές μονάδες τα τελευταία 20 χρόνια. Δυστυχώς, όμως, η διακοπή των εμβολιασμών ως αποτέλεσμα της πρόσφατης οικονομικής κρίσης, έχει επαναφέρει το πρόβλημα της νόσου ξανά στο προσκήνιο. Ο χοίρος είναι φυσικός ξενιστής του ιού και μπορεί να επιβιώσει μετά από προσβολή. Η μετάδοσή του γίνεται κυρίως με κοντινή επαφή, ωστόσο αρκετοί άλλοι τρόποι ενοχοποιούνται. Τόσο η χυμική όσο και η κυτταρική ανοσία ενεργοποιούνται κατά τη μόλυνση με τον ιό, ενώ η μητρική ανοσία μπορεί να παρέχει αποτελεσματική προστασία στα χοιρίδια, πάντα σε σχέση με τα επίπεδά της και το λοιμογόνο στέλεχος. Οι γλυκοπρωτεΐνες του ιού παίζουν, επίσης, ρόλο στην ανοσία με κυριότερο αυτό των gC και gD. Η πρόληψη και ο έλεγχος της νόσου βασίζεται στους τακτικούς εμβολιασμούς και σε μέτρα βιοασφάλειας, ενώ η εκρίζωσή της έγινε με διάφορους τρόπους ανάλογα με την κατάσταση στην περιοχή. Η ανοσοποίηση του χοίρου απέναντι στον ιό μπορεί να επιτευχθεί με τη χρησιμοποίηση ελαττωμένης λοιμογόνου δύναμης ζωντανών ή αδρανοποιημένων εμβολίων. Η ανάπτυξη της γενετικής μηχανικής οδήγησε στην παρασκευή εμβολίων, τα οποία αποτελούν σημαντικό όπλο για την αντιμετώπιση και τον έλεγχο της νόσου. Σε ό,τι αφορά την Ελλάδα, παρουσιάζεται ένα σύντομο ιστορικό και συζητείται η πιθανότητα εκρίζωσης του νοσήματος.

Λέξεις ευρετηρίασης: Νόσος του Aujeszky, επιδημιολογία, ανοσία, έλεγχος, εμβολιασμός

EPIDEMIOLOGY

ADV is spread all over the world, in parts of Europe, Southeast Asia and America. The virus has, also, been detected in Cuba, Samoa and Rwanda (Center for Food Security & Public Health 2006). In Europe, AD has been eradicated in Germany, Austria, Sweden, The Netherlands, Denmark, Belgium and the United Kingdom, while it has never been reported in countries such as Norway, Finland and Malta (Pejsak and Truszczynski 2006). In the United States of America, after application of an eradication program, all states were classified as free of the disease since June 2007. Canada and New Zealand are, also, free of ADV (Center for Food Security & Public Health 2006). Although ADV has been eradicated from many countries throughout the world, the virus is still present in populations of wild boar or feral swine. Therefore, these populations should be considered as potential ADV source of infection for domestic pigs. In countries that are free of ADV, vaccination is prohibited. Greece belongs to the countries where the disease is enzootic. According to an old serological survey in pigs in 1969, 20.8% of the collected samples from several regions of Greece were positive to antibodies against ADV. In 1983, there was an extreme increase in AD cases in the pig population following the import of breeding animals (Papatsas et al. 1995, Papadopoulos et al. 1996).

Swine is the only natural host of the virus, although ADV can infect a large number of species including cattle, sheep, goats, cats, dogs and foxes (in fur farms) as well as wildlife (raccoons, opossums, skunks and rodents). Infections in horses are rare (Center for Food Security & Public Health 2006). Despite an anecdotal report about three dubious cases of Swine Herpesvirus-1 (SHV-1) infections in man (Tischer et al. 2010), there is no evidence that it can infect humans and higher primates (Mettenleiter 2000). ADV causes neurologic disease, characterized by severe pruritus and encephalitis leading to death, in species other than pigs. The fact that the pig is the only species that can survive an ADV infection means that eliminating the virus from swine can lead to eradication of the disease (Mettenleiter 2000). Dead-end hosts such as dogs, cats or wildlife animals may transmit ADV from an infected herd to another, although these animals survive only 2-3 days after being infected.

ADV can be transmitted between swine most often via direct (nose to nose) contact (Pensaert and Kluge 1989). Transmission via inhalation of aerosolized virus can, also, occur. Contact with contaminated vaginal mucosa or semen is another likely way of infection during breeding. The fact that only a number of animals in a farm become infected with ADV supports the opinion that the virus is not as contagious as it was thought to be. The percentage of infected animals can

vary between 10% and 90% (Pejsak and Truszczynski 2006). However, during a primary outbreak of ADV in an immunologically naïve herd, the virus can spread as fast as within a week, causing abortions in pregnant sows, deaths of all newborn piglets, reduced growth and respiratory distress in fatteners (Kritas 1994).

ADV seems to be stable under various environmental conditions. It can persist for up to 7 hours in air (with a relative humidity of >55%) and it may travel through aerosols for up to 2 km depending on weather conditions. The virus can, also, survive for up to 7 hours in non-chlorinated water, for 3 days in nasal washings and for 4 days in straw bedding. ADV is inactivated by drying, sunlight and high temperatures (>37°C) due to the presence of a lipid envelope acquired from the host cell (Pejsak and Truszczynski 2006).

IMMUNITY

Infection of pigs with ADV results in an immune response, which provides clinical protection to reinfection with a virulent strain. Several factors seem to be involved in this immune response (Nauwynck 1997).

Interferon and spontaneous cytotoxicity by natural killer cells seem to participate in the early steps following infection (Martin and Wardle 1984, Wittman and Ohlinger 1985).

Antibodies against ADV can be demonstrated by serum neutralization test or by ELISA in the serum of pigs starting at 5-10 days post infection. These antibodies belong to IgM or IgG subclasses. IgM antibodies show a peak around 7 to 15 DPI and diminish to undetectable levels around 14 to 25 DPI. IgG antibodies reach their maximum around 14 DPI and persist for several months. IgA antibodies may, also, be detected from 10 DPI with a maximal titer at 13 DPI. In excretions such as saliva and tears, only IgM and IgA antibodies have been detected from 6 to 8 DPI and they reach a peak around 8 to15 DPI (Rodak et al. 1987, Kimman et al 1992a).

Neonatal piglets with colostrum-derived antibodies usually have 12-16 times higher serum neutralization (SN) titers than their mother (McFerran and Dow 1973, Kritas 1994). The SN titers of the pigs may range from 2 to 512 and seem to be higher in the litters from sows vaccinated with inactivated vaccine compared to the litters from sows vaccinated with live vaccine (Andries et al. 1978, Kritas 1994). The half-life of the colostrum-derived antibodies is 10-13 days. Maternally derived antibodies persist in the blood until 8-14 weeks of age and may interfere with the formation of antibodies at vaccination (Pensaert et al. 1982, Van Oirschot and De Leeuw 1985). High SN titers (272-354) were able to protect neonatal pigs against disease and almost entirely against neural invasion and spread upon challenge with a virulent strain of ADV (Kritas et al. 1997a, 1999a). On the other hand, low SN titers (2-3) offered clinical protection, but did not protect pigs against neuroinvasion, particularly via the olfactory pathway, which is readily accessible to the virus due to pigs anatomy (Kritas et al. 1997a, 1999a).

Suckling pigs with maternal antibodies and pigs immune after vaccination are protected against clinical disease. However, there is no definite correlation between antibody titers and protection. While some pigs with undetectable SN titers may be protected against disease, others with detectable SN titers may not (Andries et al. 1978, Van Oirschot and Gielkens 1984, Van Oirschot et al. 1984, Martin et al. 1986). The level of maternal antibodies and the virulence of the infecting strain may both play a role concerning the protection (Kritas et al. 1997, 1999). Besides, it is not always necessary that protective antibodies are neutralizing. Kritas and co-workers, after passive administration of non-neutralizing monoclonal antibodies, had shown that antibodies, are involved in protective mechanisms of the nervous tissue of the host species against spread of ADV, and particularly within the trigeminal pathway (Kritas et al. 1999c). In addition, it appears that there is no relation between in vitro neutralizing ability of antibodies and the protection that they provide against ADV spread within swine nervous system (Kritas et al. 1999c).

Antibody-dependent complement mediated lysis of ADV-infected cells and antibody-dependent cell-mediated cytotoxicity (ADCC) have been demonstrated (Ashworth at al. 1979, Martin et al. 1984, 1986, Wittmann and Ohlinger 1985). The appearance of ADCC coincides with the appearance of IgG in the serum (Wittman and Ohlinger 1985). Neutrophils, lymphocytes and monocytes are involved in ADCC (Ashworth at al. 1979).

Cytotoxic T-lymphocytes, also, seem to be involved in the immune response against ADV. Zuckermann et al. (1990) showed that infection of pigs with ADV results in the appearance of cytotoxic T-lymphocytes

specific against ADV proteins.

Glycoproteins have been identified as the major antigenic proteins of ADV (Todd et al. 1987). Glycoprotein gC seems to be a major immunogen of ADV, since in sera of pigs that recovered from ADV infection, a major fraction of the neutralizing activity was directed against gC (Ben-Porat et al. 1986). Monoclonal antibodies against gC may neutralize ADV without complement (Humpl et al. 1984, Wathen et al. 1985, Marchioli et al. 1988) and passive immunization with some anti-gC monoclonal antibodies protects pigs against lethal ADV infections (Marchioli et al. 1988). Experiments have shown that gC is more important than gE, gI or gG with regard to the induction of cytotoxic T lymphocytes of pigs (Zuckermann et al. 1989b, 1990). In mice, active immunization with a gC^- mutant was markedly less effective in eliciting neutralizing antibodies, cytotoxic T-lymphocytes and protection against challenge compared to immunization with gE-, gI- or gG–negative mutants (Zuckermann et al. 1989b, 1990).

Glycoprotein gD is, also, a major immunogen of ADV. Monoclonal antibodies against gD can neutralize ADV without complement (Eloit et al. 1988, Coe and Mengeling 1990) and can passively protect pigs against lethal ADV infections (Marchioli et al. 1988). Active immunization of pigs with gD resulted in production of neutralizing antibodies and conferred protection against ADV infection (Marchioli et al. 1987, Mukamoto et al. 1991). Suckling piglets born from sows previously immunized with gD glycoprotein had neutralizing antibodies in their blood and were protected against virulent virus (Mukamoto et al. 1991).

Glycoprotein gB is, also, involved in the development of immunity against ADV. In sera from infected pigs, a fraction of the neutralizing activity was directed against gB (Ben-Porat et al. 1986). Monoclonal antibodies against gB may neutralize ADV without complement (Wittmann and Rziha 1989) and may confer passive protection to pigs against lethal ADV infection (Marchioli et al. 1988).

Glycoprotein gE seems to play a less important role than gC and gB in immunity against ADV. Ben-Porat and co-workers (1986) have shown that convalescent pig sera have no or little neutralizing activity against gE. Monoclonal antibodies directed to gE neutralize ADV in the presence of complement (Eloit et al. 1988). Passively administered anti-gE monoclonal antibodies protected mice against ADV lethal infection (Fuchs et al. 1990), while no data are available in pigs.

Anti-gI monoclonal antibodies do not neutralize virus in the absence of complement (Eloit et al. 1988).

Glycoprotein gG does not induce neutralizing antibodies and immunization of mice with gG, it did not protect against lethal ADV infections (Thomsen et al. 1987).

PREVENTION AND CONTROL

The prevention strategy against AD is characterized by control measures such as stamping out infected herds, test-and-removal of infected pigs, vaccination programs or a combination of these above measures (Stegeman 2000). These are escorted by restriction of swine movements, decontamination and disinfection of material and equipment, biosecurity procedures for persons with access to pigs and facilities, as well as rat control strategies. Domestic animals other than swine, such as dogs and cats, should be kept out of the facilities, as they may be infected with the virus and transfer it to the herd.

However, the principal control measures depend on the situation found in every country or area:

1. In countries free of ADV, depopulation of any infected herd is the only choice, in addition to strict biosecurity and prevention measures (Pejsak and Truszczynski 2006).

2. In countries or areas not yet free of ADV, but with the intention to become free, primary reduction of the virus spread by systemic vaccinations with DIVA (Differentiating Infected from Vaccinated Animals) vaccines at least for 3 years is necessary. All breeding animals, as well as the nursery pigs, need to be regularly vaccinated until less than 10% of the sows and none of the fattening pigs are tested infected. Intensive testing of the animals for the presence of virulent ADV with a differentiating ELISA and their removal will eventually establish an ADV-free status (Pejsak and Truszczynski 2006).

3. In some countries, vaccination is not followed by the removal of positive animals. In that case, although AD might be present, there are no clinical signs of the disease. The application of a vaccination program in

those countries is crucial for the control of the disease. Vaccination against ADV will "keep down" the manifestation of typical clinical signs without eradicating the disease (Papatsas et al. 1995).

VACCINATION

The cornerstone for the control of AD is vaccination. In general, vaccination reduces the clinical signs of ADV, although it does not prevent the spread and the development of latent infection by the virulent virus. The aim of vaccination in an eradication campaign is not only to induce clinical protection, but primarily to stop transmission of infections within and between herds by inducing herd immunity. Both attenuated and inactivated vaccines can be used (Kritas 1994). In ADV endemic areas, it is strongly recommended that all newly induced breeding animals in the herd should be vaccinated, while breeding animals must be vaccinated regularly. In addition, piglet vaccination can further assist against the circulation of the virus in the herd. Vaccination of pigs must be implemented at 10 and 14 weeks of age, if they are born to vaccinated sows, or at 6 and 10 weeks of age, if they are born to unvaccinated ones (Pejsak and Truszczynski 2006).

The development of marker vaccines and the use of diagnostic tests (differential ELISA) can play an important role in disease eradication and control programs, as it was determined in the ADV eradication program in the U.S. (Foley et al. 2005). During that campaign, the use of gene-deleted vaccines in conjunction with diagnostic tests was able to differentiate infected from vaccinated animals, in a strategy that finally led to eradication of the disease from swine herds (Foley et al. 2005). In The Netherlands, in which an eradication campaign was developed in 1993, ADV was eradicated in 2002, as shown by the absence of gE-positive pigs (Bouma 2005).

The development of genetically engineered vaccines against ADV has been one of the most important factors in the control of the disease (Kritas et al. 1997b). Such vaccines are produced by the deletion of specific genes from the genome of the virus. The deleted genes encode certain proteins that determine the virulence of the strain, while they are not responsible for the induction of immunological response. Although the role of gE is not fully established, it is believed that gE plays an important role in the transmission of ADV between cells and the movement of ADV in the neurons. In addition, TK enzyme is necessary for the replication of ADV in the neurons (Kit et al. 1985, Tenser 1991, Kritas et al. 1999b). Therefore, deletion of both these proteins results in a high degree of vaccine attenuation and a live vaccine safe for the pigs. Besides genetically engineered deletion mutant vaccines, there are live vaccines containing gE-strains that have been attenuated by natural methods, such as the continuous passages through cell cultures (Bartha strain). In recent years, the emergence of DNA vaccines may play an important role in the prevention of ADV infection in the future. According to Rooij et al. (2005), the DNA vaccination with a plasmid encoding gD of PRV in pigs provides protective immunity against the infection with a wild virus strain.

The situation in Greece and the possibility of a national eradication program.

Up to 1973, sporadic cases of AD in bovine, sheep and mink had been diagnosed in Greece. According to a serological survey in pigs from several regions of Greece in 1969, 20,8% of the collected samples was positive to antibodies against ADV. The first clinical report with virus isolation in this species was on May 1974. Two more clinical cases with high mortality of suckling piglets had been reported on January 1976 and February 1977. In 1983, scattered outbreaks of the disease in all territory had followed the import of breeding animals from other European countries. The first measures were isolation of the affected herds and vaccination of all healthy herds with inactivated or attenuated vaccines (Papadopoulos 1989, Papatsas et al. 1995, Papadopoulos et al. 1996).

Greece has many important advantages over several European countries, which had already eradicated ADV (Papadopoulos et al. 1996):

- The low density of the pig population (7 pigs/km^2 in Greece, when in Holland it is 400 pigs/km^2, in Belgium 230 pigs/km^2, in Germany 73 pigs/km^2, in Italy, Portugal, Spain and France between 20 and 30 pigs/km^2).
- The type of the units is principally farrow-to-finish having their own feed mill. Thus, entrance of virus in the farms can be better prevented when compared to the fattening type of units.
- As a country that imports most of its breeding

stock, an ADV-free status of animals can be required from breeder countries.

- Vaccinations with live or inactivated gE^- vaccines are regularly applied in the majority of the organized farms.

Unfortunately, no national strategies for the eradication of ADV have ever been applied in Greece. Vaccination against ADV supresses the manifestation of typical clinical signs. This fact combined with the recent economical crisis has led some farmers to abandon vaccination against ADV. It is important to keep in mind that vaccination does not eliminate the virus and that latent virus will "come up" in the population when a "chance" will occur. Indeed, the presence of a virulent ADV strain was recorded in many farms requiring health management assistance after non-response to intensive treatments (Kritas et al. 2011). All these farms had a history of interruption in their AD vaccination program. In most of these cases, weight gain depression and respiratory signs in fatteners, or manifestation of reproductive problems were observed (Kritas personal communication).

Based on our health management experience, we recommend and encourage farmers on the following main issues:

- Systematic application of gE^- vaccine (live or inactivated) on the breeding stock and the fatteners (live vaccine) of the farm.
- The purchase of only gE^- replacement stock.
- Supportive measures such as application of "all-in, all-out" system, strict biosecurity/ quarantine measures for animals and visitors, prevention of stressy conditions.
- In the case that farmers wish to quit ADV vaccination, this should be done not based on clinical or post mortem findings, but on intense laboratory testing of the current and incoming stock. A qualified herd health management specialist on infectiology should direct such procedures plus all appropriate additional measures.

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