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REVIEW

CORONAVIRIDAE, PATHOGENETIC AND CLINICAL ASPECTS: AN UPDATE

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Abstract—A review is given about pathogenetic and clinical aspects of the well-known as well as of recently detected members of the family Coronaviridae. Special attention is paid to coronavirus infections of domestic cattle and pets, whereas avian, murine, rat and human coronaviruses are summarized briefly.

Key words: Coronaviridae, pathogenesis, clinical aspects.

REVUE ACTUELLE SUR LES VIRUS DE LA FAMILLE CORONAVIRIDAE, LEURS ASPECTS DE LA PATHOGÉNÈSE ET DU COURS CLINIQUE

Résumé—Le présent article décrit la pathogénie et la clinique des membres de la famille Coronaviridae bien connus ainsi que ceux dépistés récemment. Les coronavirus du bétail et des petits animaux domestiques sont traités en détail, tandis que ceux des volailles, des rongeurs et de l'homme sont résumés brièvement.

Mots-clefs: Coronaviridae, pathogénie, cours clinique.

INTRODUCTION

Coronaviruses represent a large family of mammalian and avian pathogens, first described in 1968 [1]. As several members of this virus group are known to cause economically important diseases, much effort was put into research during the last years. Special reviews cover the replication strategy of coronaviruses [2], their glycoproteins [3] and their structure and genome expression [4]. The recent detection of previously unknown coronaviruses or mutants, like the "Porcine Epidemic Diarrhea"-virus (PEDV) and the TGE-like "Porcine Respiratory Coronavirus" (PRCV) on one hand and new knowledge about pathogenetic mechanisms, for example in FIPV-infections, on the other hand are the basis for this review article.

Coronaviruses are pleomorphic particles with a diameter of 60–220 nm, possessing typical club-shaped spikes. Their physicochemical and biological properties and antigenic relationships were reviewed by Wege *et al.* [5]. Antigenically they are grouped into 4 classes:

Group 1: Transmissible Gastroenteritis Virus (TGEV), Canine Coronavirus (CCV), Feline Infectious Peritonitis Virus (FIPV), Human Coronavirus (HCV)-229E;

Group 2: Hemagglutinating Encephalomyelitis Virus of pigs (HEV), Bovine Coronavirus (BCV), Murine Hepatitis Virus (MHV), Rat Coronavirus (RCV), Human Coronavirus (HCV)-OC43;
Group 3: Infectious Bronchitis Virus (IBV);
Group 4: Turkey Coronavirus (TCV).

However, highly sensitive techniques like immunoblotting revealed some discrepancies. An antigenic relationship was detected between a MHV strain and HCV-229E, a MHV strain and IBV and between FIPV and HEV (see Ref. [6]). While the antigenic classification of PEDV still remains unclear, an antigenic cross-reaction at the nucleocapsid level between PEDV and FIPV was detected [6].

PORCINE CORONAVIRUSES

There are three known porcine coronaviruses: Transmissible Gastroenteritis Virus (TGEV), Porcine Epidemic Diarrhea Virus (PEDV) and Hemagglutinating Encephalomyelitis Virus (HEV).

Recently, a virus antigenically related to TGEV spread through the European swine population. It infects only the respiratory tract and is therefore called "Porcine Respiratory Coronavirus" (PRCV) or "respiratory variant of TGEV".

TRANSMISSIBLE GASTROENTERITIS VIRUS (TGEV)

Transmissible gastroenteritis (TGE) was first described by Doyle and Hutchings [7]. The classical enteric variant of TGEV is an enteropathogenic agent causing severe diarrhea. Although swine of all ages are susceptible to infection, the most severe clinical symptoms are observed in newborn piglets reaching a mortality rate of about 100%. With increasing age the mortality rate declines due to age resistance and is very low in pigs over 5 weeks of age.

The virus usually enters by the oral route. It is able to resist the low pH of the gastric juices, reaches the small intestine and destroys the villous enterocytes causing atrophy of the villi. The resulting acute malabsorption syndrome is the consequence of a reduced enzymatic activity and cellular transport of nutrients and electrolytes of the damaged villous enterocytes. The replacement of villous epithelium in the small intestine is markedly accelerated in animals of 3 weeks and older compared to newborn pigs. The young villous cells produce less virus resulting in an age-dependent resistance to TGE [8]. Furthermore, an impaired lymphocyte cytotoxicity was found in newborn piglets and was accounted for the high susceptibility to TGEV during the first weeks of life [9].

The clinical signs in piglets usually are vomiting, followed by a watery yellowish diarrhea, loss in weight and dehydration. For details see Pedersen [10]. In animals younger than 7 days death occurs about 2–7 days after the onset of disease. In older pigs inappetence and diarrhea of short duration are observed, but subclinical infections also occur. Sometimes lactating sows show severe clinical signs including vomiting, diarrhea, fever and agalactia. The incubation period varies between 18 h and 3 days.

In a susceptible herd TGEV spreads very rapidly to animals of all ages. This epizootic form usually lasts a few weeks, but may persist in an enzootic form, if susceptible animals are continually present [10]. Most sows of such herds are infected and thereafter provide

passive immunity to their suckling piglets, which are protected to a variable degree. Under such conditions diarrhea especially occurs after weaning [11].

Colostrum and milk of immune sows contain high titres of antibodies especially of the IgA class (see Ref. [10]), which protect piglets provided that the antibodies are in continual contact with the enterocytes of the gut mucosa. The term "lactogenic immunity" was coined by Haelterman [12].

Active immunity is only acquired by gut infection resulting in the production of IgA. Sensitized lymphocytes migrate from the gut to the mammary gland leading to local IgA production in lactating sows (gut–mammary immunologic link). After parenteral inoculation of TGEV only antibodies of the IgG class are produced, which mediate merely poor protection.

In order to induce maternal immunity sows may be infected with virulent TGEV at least 3 weeks ante partum (planned infection). Gut material of piglets which died in the acute phase of TGE is fed to sows. As this procedure includes some disadvantages such as the possible transmission of other pathogenic agents, much effort has been made in order to develop other effective vaccination procedures in pregnant sows. None has proved satisfactory (see Ref. [10]). However, oral application of live, nonattenuated virus resulted in elevated titres of protective milk-antibodies for 21 days after farrowing [13].

For diagnosis TGEV antigen can be detected by immunofluorescence in the small intestine of piglets at an early stage of disease, by virus isolation in tissue culture or by ELISA. For serological investigations the neutralization test is frequently used because of its sensitivity and reliability.

PORCINE RESPIRATORY CORONAVIRUS (PRCV)

In 1986 a variant of TGEV was isolated in Belgium [14] and Great Britain [15]. As it causes a respiratory infection and does not replicate in the enteric tract, it was named "Respiratory Variant" of TGEV [16] and recently "Porcine respiratory coronavirus". It spreads quickly in the swine population, probably by an aerogenic route, replicates in the nasal mucosa, trachea and lungs and usually does not cause clinical signs [14, 16]. Recent studies, however, demonstrated that the virus can cause pneumonia [17]. Antibodies produced in infected animals cannot be differentiated from antibodies against the classical TGEV by serum neutralization test. This fact causes problems in the sectors of import and export certificates. Recently, using monoclonal antibodies an antigenic difference was demonstrated between TGEV and PRCV concerning an alteration of the E2 protein portion [18]. It is the basis for an ELISA distinguishing between antibodies against the two variants of TGEV.

According to Hooyberghs *et al.* [19] PRCV-seropositive sows do not mediate protection to their piglets against TGEV-field infection, whereas Bernard *et al.* [20] described such a protection under experimental challenge conditions.

PORCINE EPIDEMIC DIARRHEA VIRUS (PEDV)

Diarrhea in pigs very similar to TGE was described in Great Britain [21]. A "coronavirus-like" agent was identified as causative virus in 1978 [22, 23], that was different from the other known porcine coronaviruses. It was named PEDV, in Germany

the name "Epizootische Virusdiarrhoe" (EVD) was proposed [24], in France Vannier and Debouck [25] called it "Diarrhée épidémique porcine" (D.E.P.).

The pathogenesis of PED is very similar to that of TGE. The epithelial cells both of the small and partly of the large intestine are destroyed resulting in villous shortening. After an incubation period of 22–48 h the clinical signs consisting of diarrhea, vomiting and dehydration appear and are hard to differentiate from those of TGE [26]. Contrarily to TGE, weaned and feeder pigs are the most affected groups [26]. In previously uninfected herds, however, PED may result in severe clinical disease in suckling piglets and mortality rates of up to 90%. In general, TGE spreads more quickly in infected herds causing a more severe syndrome [26], but Heinritzi *et al.* [11] described that during the last years cases of TGE, they often showed an altered clinical course, more and more similar to PED.

Very similar pathogenetic mechanisms of PED and TGE cause the same immunological situation. Protection against PED is based on intestinal mucosal immunity, which is limited to a short period after infection. Lactogenic immunity, but not circulating antibodies are protective for suckling piglets. There are no vaccines available.

For diagnosis virus antigen is detected by immunofluorescence (see Ref. [26]) or by a blocking-ELISA [27].

VOMITING AND WASTING DISEASE (VWD), HEMAGGLUTINATING ENCEPHALOMYELITIS VIRUS (HEV)

HEV was first isolated from the brain of a suckling piglet with encephalomyelitis [28]. Later a virus was detected in animals with VWD that was antigenically related to HEV [29]. Mengeling and Cutlip [30] identified HEV as a responsible agent for the encephalomyelitis as well as for VWD.

The virus is probably transmitted through nasal secretions [31]. It first replicates in the upper respiratory tract, in general without inducing clinical symptoms. Subsequently it spreads via peripheral nerves to the central nervous system causing either encephalomyelitis or VWD. Severe clinical signs are seen almost exclusively in piglets younger than 3 weeks. After an incubation period of 4–7 days they show repeated vomiting, are listless and pale and huddle together. Andries [32] postulated that vomiting is caused by viral replication in the vagal sensory ganglion or by infected neurons affecting the vomiting center. In the course of encephalomyelitis generalized muscle tremors and hyperesthesia are commonly observed, sometimes blindness, opisthotonus and nystagmus occur. Weakness is followed by coma and death is observed in most of the young animals. The wasting was assumed to be caused by a disturbance of stomach emptying [32].

Although HEV is distributed worldwide among pig populations, clinical disease occurs seldom. As most sows are seropositive, their piglets are protected by maternal antibodies till an age-dependent resistance has developed. During the phase of passive immunity subclinical infections occur inducing an active immunity in pigs 8–16 weeks of age (see Ref. [31]). In order to avoid clinical signs in piglets it is favorable to obtain immune sows at the time of farrowing.

For diagnosis virus may be isolated from the tonsils, the brain and lungs of diseased piglets by cultivation in several tissue culture systems. For serological investigations the hemagglutination-inhibition- or seroneutralization-test are commonly used.

BOVINE CORONAVIRUS (BCV)

A coronavirus-like agent was detected in the feces of a calf with diarrhea [33, 34] and characterized as coronavirus [35]. BCV was recognized as an economically important infectious agent producing diarrhea in newborn calves. Later it was identified to have a second tropism in being involved in respiratory disease in older calves [36].

After peroral incorporation BCV infects villous and to some extent crypt enterocytes. Following experimental inoculation lesions in the small intestine were observed similar to those described for TGE in pigs [37]. After an incubation period of 18–36 h severe, often watery diarrhea is observed [33]. In some cases an extensive loss of water and ions causes death. In some investigations the highest incidence of coronavirus-induced diarrhea was found during the second and third weeks of life, whereas other authors observed the most severe cases during the first week of life (see Ref. [38]).

As a typical enteric viral infection, bovine coronavirus infection can be prevented by passive local immunity (lactogenic immunity), whereas no or limited protection is mediated by serum antibodies. The mammary secretions of seropositive dams contain specific coronavirus-antibodies, which, contrary to the swine, belong to IgG1 as the major isotype [39]. For effective protection these antibodies have to be continuously present in the calf's gut lumen. But contrary to monogastric animals in cattle elevated antibody titres are only present in the colostrum and decrease sharply upon transition to milk. In parallel, protection against enteric infections declines. Many attempts were made to enhance lactogenic immunity against coronavirus as well as rotavirus, a pathogenetically very similarly acting enteric viral pathogen.

In order to prolong the protective effect of colostral antibodies first-day colostrum of seropositive cows was fed to calves, which proved beneficial if originating from vaccinated dams [40], but not from field-infected cows [38]. Most efficacious, however, is active vaccination of cows late in pregnancy. As on premises with enzootic infections almost all cows possess antibodies, a booster reaction occurs after parenteral vaccination resulting in a more effective and longerlasting lactogenic immunity. The route and time of immunization, the adjuvant used and the viral dose and form (live or inactivated) are of remarkable influence (reviewed in Ref. [41]). Some authors demonstrated significantly enhanced antibody-titres in mammary secretions of intramuscularly vaccinated cows, whilst other authors did not (see Ref. [42]). In our investigations significant increases were not found either, although remarkable protective effects were shown by clinical and virological parameters [42]. Attempts to immunize calves actively by the oral route were unsuccessful under field conditions because of interference with maternally-derived antibodies [43, 42].

The involvement of BCV in respiratory tract affection was first described by Thomas *et al.* [36]. Coronaviruses were isolated in calves with non-febrile rhinitis and cough [44] as well as in cases of severe pneumonia [45]. In the course of two outbreaks of respiratory disease both syndromes occurred in an enzootically infected herd [46]. Remarkably, calves with persisting maternal antibodies were not affected, whereas older calves whose titres had just decreased fell sick. Investigations performed by Reynolds *et al.* [47] indicated that enteric as well as respiratory infection was caused by a monotypic BCV. So it was assumed that active vaccination of older calves might prevent clinical disease on premises affected by the respiratory form of BCV [46].

Since enteric viral agents are difficult to propagate in cell cultures, diagnosis first was performed by electron microscopy. The development of an ELISA permitted detection of rota- and coronavirus antigen in fecal samples [48].

FELINE CORONAVIRUSES

A disease syndrome consisting of inflammation of the visceral serosa and exudation into the body cavities, called Feline Infectious Peritonitis (FIP), was first described by Wolfe and Griesemer [49]. Montali and Strandberg [50] observed a second form, characterized by granulomatous inflammation in several parenchymatous organs. In order to differentiate the two forms the first one was called "wet" or "effusive", the second one "dry" or "noneffusive". A viral agent morphologically similar to other coronaviruses was demonstrated and later characterized as a member of the family Coronaviridae (see Ref. [51]).

Many years later a feline coronavirus was isolated from mild enteral infections and was called feline enteric coronavirus (FECV). It was shown to be very closely related to FIPV [52].

FELINE INFECTIOUS PERITONITIS (FIP) AND FELINE ENTERIC CORONAVIRUS (FECV)

FIPV is distributed worldwide, but compared to the high percentage of seropositive cats, clinical disease is observed relatively rarely. Strains of feline coronaviruses vary greatly in infectivity and virulence and may either induce FIP or enteritis. Strains causing enteritis are very infectious and therefore widely distributed. They are of low pathogenicity but induce the production of circulating antibodies. FIPV strains, however, vary extremely in infectivity and virulence and only some of them cause typical signs of FIP [51]. By using monoclonal antibodies two antigenic types of feline coronaviruses with marked difference in the peplomer (E2) glycoproteins were found [53]. These two types correlated well with virulent or avirulent isolates.

Although there are a few cases described with evidence for in utero infection (see Ref. [51]), the most frequent route of infection is probably the oral ingestion, followed by virus replication in the intestinal epithelium. Whereas FECV strains do not spread wider than into the lymph nodes, FIP-causing virus strains have a tropism for phagocytic cells. They replicate in macrophages and are disseminated by them. Pedersen [51] assumed that not only the properties of the infecting virus strain were responsible for the outcome of the disease, but that also the immunologic situation of the host and the type and degree of developing immunity may be of great importance. While humoral antibodies were shown to enhance the development of clinical disease (see Ref. [51]), immunity to FIP seems to be cell-mediated. Pedersen [51] proposed a scheme for the pathogenesis of FIP: a strong humoral, but lacking cellular immunity is assumed to be responsible for development of effusive FIP. Strong humoral and weak cellular immunity may lead to noneffusive FIP. A strong cellular immunity, however, may inhibit the development of disease. Weiss and Cox [54] demonstrated delayed-type hypersensitivity-like reactions to FIPV in the skin of cats which had remained asymptomatic after a previous challenge-exposure with FIPV. The assumption is supported by the fact that cats having recovered from FIPV infections and harboring the virus in a latent form often develop clinical FIP after a coinfection with

feline leukemia virus (FeLV), that mainly depresses the cellular immunity. In general a high percentage of cats with naturally occurring FIP is coinfected with FeLV.

After an incubation period of some weeks to months the clinical signs of FIP-disease start with chronic fever, accompanied by a progressive decline in the general condition. Effusive FIP is characterized by peritonitis and ascites and/or pleuritis causing pleural effusion and dyspnea. The peritoneal and pleural fluids as well as the blood serum contain very high levels of protein, especially of the beta and gamma globulins (see Ref. [51]), the visceral serosa of the abdomen and the thorax show pyogranulomatous lesions. In cats with noneffusive FIP the clinical signs are variable depending on the affected organ systems, where typical granulomatous lesions have developed. Frequently ocular and CNS signs are observed. Clinical illness lasts for 1–6 weeks (in cats with noneffusive form also for a longer period) and usually leads to death. Contrary, infection with FECV remains subclinical in most cats or induces only mild diarrhea. Pedersen *et al.* [52] assumed that many cats are virus carriers shedding FECV in their feces and that often kittens are infected after weaning.

After infection with feline coronaviruses antibodies appear in the serum of clinically ill cats as well as of animals remaining healthy. Frequently, but not always, there are very high anti-FIPV-titres in the diseased cats. These as well as non virus-specific globulines lead to a characteristic hypergammaglobulinemia. Antibodies play an important role in the pathogenesis of FIP by leading to the development of circulating immune complexes which are deposited in several organs. Such immune complexes were shown to consist of viral antigen, IgG and complement (see Ref. [51]). Horzinek and Osterhaus [55] justly interpreted FIP as an immune-complex disease.

The role of humoral antibodies in FIP pathogenesis and the unknown mechanism of immunity result in the lack of an effective vaccine. Immunization with attenuated as well as inactivated virus strains does not mediate protection but on the contrary enhances clinical disease following virus exposure. Heterotypic vaccination with for example TGEV was not protective against FIPV challenge (see Ref. [51]). Recently, however, Christianson *et al.* [56] characterized a temperature sensitive FIPV, which propagates at 31°C, but not at 39°C. It is avirulent, replicates only in the upper respiratory tract and the authors described that this mutant is able to stimulate protective immune responses without inducing sensitization of the cat.

Furthermore, consistent vaccination against FeLV is expected to reduce the occurrence of clinical FIP by eliminating the suppression of the cat's immune response towards FIP caused by FeLV infections.

Although presently most of the cats which have developed clinical signs of FIP will die, sometimes spontaneous remission is observed. There is no consistently effective treatment available. In some cats therapeutic success may be achieved by application of glucocorticosteroids because of their immunosuppresive effect, but in most cases the fatal course of the disease is only prolonged [51].

As a diagnostic aid serological tests are used. A heterologous indirect immunofluorescence assay was developed by Osterhaus *et al.* [57] using TGEV-infected cells as antigen, later ELISAs became commercially available. However, neither test allows differentiation between cats infected with FIPV or FECV and between virus shedders and non-shedders. The test result often is helpful in ascertaining diagnosis in clinically sick cats, as animals with acute FIP usually develop very high titres. On the other hand a significant decrease of titre may be observed in preterminal stages. Unfortunately, relatively high titres may

also occur in healthy cats with subclinical or latent infections. Because of these difficulties interpretation of serological tests offers limited value to the clinician. The tests are, however, helpful for screening purposes and epidemiological investigations.

Recently, Walter *et al.* [58] reported a modified Avidin–Biotin–Peroxidase-Complex-method in order to demonstrate viral antigens in paraffin sections of tissues of FIPV-infected carcasses.

CANINE CORONAVIRUS (CCV)

Epizootics caused by CCV were reported in Germany [59] and in U.S.A. [60]. In most cases a mild gastroenteritis was the only symptom recorded, but especially in younger pups more severe signs of disease were observed. As indicated by serological investigations CCV is widespread within canine populations. In Germany a seroprevalence of 50% was described [61], but only in 12% of diarrheic feces coronaviruses were detected [62]. Distress and several infectious agents aggravate clinical disease by contributing to the "canine enteritis complex" [63].

After oral inoculation of CCV the enterocytes of the intestinal villi are infected leading to villous atrophy. As the infection does not spread further than to the mesenteric lymph nodes, no viremia occurs. After an incubation period of 1–7 days clinical signs consist of diarrhea, vomiting, depression, anorexia and dehydration [64].

Similar to other typical enteric viral infections the local immunity of the gut appears to be responsible for protection [64]. After infection with CCV low serum antibody titres develop that do not mediate immunity. A killed CCV vaccine is currently under investigation for its effectiveness (see Ref. [63]).

MURINE CORONAVIRUSES (MHV)

Many different murine coronavirus strains have been described, the first one was isolated from a spontaneously paralyzed mouse [65]. Infections with MHV often take a subclinical or inapparent course. Depending on the virus strain, the age of the affected animal, its genetic background and immunological situation, disease occurs resulting in acute fatal hepatitis or encephalomyelitis or enteritis. The infection of the nervous system takes place by invasion via the olfactory nerve after an initial replication in the nasal mucosa and is characterized by an acute or chronic demyelinating disease. Enteropathogenic strains of MHV cause an acute intestinal disease with a high mortality rate during the first 3 weeks of life. The aspects of infections with MHV were reviewed by Wege *et al.* [5].

RAT CORONAVIRUSES

Two virus strains have been reported, the first infecting the respiratory tract and causing respiratory disease, especially during the first 48 h of life. In animals older than 7–14 days the course of the disease is mild or clinically inapparent [66]. The second virus strain affects the salivary and lacrimal glands leading to sialodacryoadenitis with rhinitis [67].

AVIAN CORONAVIRUSES

Infectious bronchitis virus (IBV) is an economically important pathogen for the chicken raising industry. It causes respiratory disease, which was already described in 1931 [68] and is distributed worldwide. At least 8 serotypes of IBV have been described. After infection of the respiratory tract, usually by aerogenic spreading, the virus also replicates in the kidneys, the ovaries and oviduct. The clinical signs consist of tracheitis, bronchitis, decrease of egg production and egg quality. Sometimes nephritis is observed. The most severe disease occurs in chickens up to an age of 5 weeks with a mortality of 40–90%, whereas in older animals IBV infection takes a milder course. For prophylactic purposes modified live vaccines are applicated by drinking-water.

Turkey coronavirus (TCV) was identified as the aetiologic agent of the transmissible enteritis of turkeys [69]. While the infection takes a mild course in older animals, turkeys between 1 and 6 weeks of age develop depression, loss of appetite and weight and watery diarrhea. Ensuing circulation disorders mediate the typical syndrome "bluecomb disease". The pathogenetic mechanisms are very similar to other enteric coronavirus infections resulting in villous atrophy. Protection is only achieved by local immunity. For a comprehensive review of clinical signs, pathogenesis and immunology of avian coronaviruses see Wege *et al.* [5].

HUMAN CORONAVIRUSES (HCV)

Human coronaviruses are distributed worldwide. They infect the respiratory tract and are responsible for common colds [70], in children pneumonia may be observed. Additionally, coronavirus-like particles were detected in diarrheal stool specimens from humans [71] and primates [72].

ISOLATES PROBABLY BELONGING TO CORONAVIRIDAE

In the U.S.A. coronavirus-like particles were demonstrated in the feces of foals suffering from severe diarrhea [73]. Huang *et al.* [74] isolated a coronavirus-like agent from horses suffering from acute equine diarrhea syndrome, called "Potomac fever". Horses of all ages were affected showing fever, inappetence and diarrhea followed by death in about 25% of the cases.

CONCLUSIVE REMARKS

Coronaviruses show different organ tropisms, mainly resulting in three disease complexes: gastrointestinal disease, respiratory disease and generalized disease. The different pathogenetic mechanisms implicate distinct immunological situations. The important role of the local immunity in enteric infections has been well documented. In newborn animals protection by lactogenic immunity can be enhanced by vaccination of the dam quite successfully in the bovine and to a lesser extent in the sow. FIPV-infections, however, are crucial at present with regard to prognosis as well as immunoprophylaxis. Maybe virus mutants with specific tropisms will offer new aspects for vaccination, as for example PRCV against TGE and the ts-mutant against FIP.

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