PATHOGENESIS AND EPIDEMIOLOGY OF HOG CHOLERA

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Résumé

PATHOGÉNIE ET ÉPIDÉMIOLOGIE DE LA PESTE PORCINE CLASSIQUE. — Un aperçu est donné sur l'infection par le virus de la peste porcine classique, infection résultant en différentes formes de la maladie dues à la variabilité du virus et de l'hôte. Les mécanismes par lesquels le virus induit une mort prénatale ou une maladie postnatale chez le porc sont pris en considération. L'épidémiologie caractéristique relative aux différents aspects de l'infection et aux différentes formes de la maladie résultant du contact pré- ou postnatal avec le virus est discutée.

1. Introduction

Historically, the term hog cholera (HC) refers to a serious disease which appears to have produced fatal losses up to 27 % of the pig population in some parts of the United States during the second half of the last century. In Europe, it took some time before it was recognized that "swine fever" known in England since 1862, "Swinpest" in Sweden, "pneumo-entérite infectieuse" in France, and since 1887 "swine-diphterie" in Denmark and "Schweineseuche" in Germany were identical with "hog cholera", "pig fever" or "swine plague" as the disease was called in the United States.

While still in the bacteriological era Zschokke (1895) at the 6th International Veterinary Congress held in Berne, reviewed the evidences as to the identity of the various disease entities reported so far. Apart from detailed clinical and pathological descriptions of the disease in its acute or peracute form, Zschokke also refered to chronic cases following acute illnesses. He also admitted that the «Schweineseuche» first observed in 1892 might have been misdiagnosed formerly as Erysipelas.

Zschokke's paper can be regarded today as a document on the confusing situation as it existed before De Schweinitz and Dorset (1903) discovered that a filtrable agent was responsible for hog cholera, and hence for many of the disease incidences reported from the various parts of Europe.

Since then it was no longer justified to refer to hog cholera as a disease only instead of a particular infection caused by a particular virus.

The discovery of the viral origin opened the field for etiological studies on hog cholera. However, it was not before the early 1960th that a workable specific system by using fluorescent antibodies became available for the detection of HC viral antigen in organ tissues (Stair *et al* 1963) and in cell culture systems after virus multiplication (Solarzano 1962).

Although different courses of hog cholera were apparently known since the last century, later it was learned that differences in virulence existed amongst strains of HC virus. The classical course of infection terminating in death between 10 and 20 days after exposure (or even earlier in peracute cases) and counting for the most impressive losses within a short period of time led to the introduction of the term "classical swine fever (CSF)".

The more protractive courses of infection did not attract much interest before it was realized that HC virus was not only responsible for the classical course, but also for congenital infections with a variety of signs being observed in the litters (Young *et al* 1955). Last not least, piglets after prenatal contact with the virus were observed being persistently infected in some cases without clinical signs (for review: Liess 1984).

2. Pathogenesis

The term pathogenesis can be defined as the mechanism(s) by which an agent causes disease (Parsonson and McPhee 1985). Factors which are required for the initiation of an infection eventually resulting in disease are the following:

1. Virus
— minimal infectivity
— some virulence
— transfer to host on natural routes

— direct or indirect interaction with host organ systems

2. Host

— susceptible cells at organ of entry
— broad spectrum of susceptible cells
— spreading of virus via circulatory system
— target cells responsible for vital systemic functions

2.1. Factors related to hog cholera virus

Experimental data obtained from simultaneous hog cholera virus titration in weaner pigs and PK(15) cell cultures showed that there was good correlation in titers of the high-virulence "Alfort" strain of HC virus. In addition it could be concluded that the minimal infective dose resulting in fatal disease was less than 10 TCID50 per pig. At the highest log10 dilution step of virus at which fatal disease occurred in 1 out of 4 animals, the 3 surviving pigs developed high neutralizing antibody titers without clinical disease. This shows that even high virulence virus does not necessarily result in a fatal course of infection with hog cholera leaving open the question : how can the term "virulence" be defined in general and in relation to hog cholera in particular ?

It is well known that there is an age-dependence as to the reaction of pigs towards HC virus thus giving reason to expect that pigs, eg, in breeding age might be infected by contact without developing clinical symptoms suspicious of hog cholera.

Very little is known about differences in their pathogenic properties of strains of HC virus beyond the empirical observations that they have been derived from cases of fatal hog cholera in older pigs indicating postnatal infection or infections of newborn piglets with their dams not showing any signs of illness. In this latter case, it has often been assumed that the pregnant sow upon infection fell not ill because of low-virulence of the HC virus strain involved. This conclusion might prove to be wrong but shows that systematic investigations have still to come in order to elucidate the term "virulence" in the field of hog cholera. Markers like growth requirements, eg, suboptimal temperature for low-virulence strains of HC virus as described by Aynaud (1968) might be helpful but seem to necessitate further evaluation with the inclusion of a number of authentic field strains of virus.

The mode of transfer of virus to the host organism appears to influence the outcome of the infection, too, again in the light of possible overdosing by "needle" inoculations in relation to low doses of virus which are acquired by contact from an infected pig.

The most frequent natural route by which HC virus enters the host is oronasal. Genital contact with infected boars will also mediate infection in sows. Considering the whole life cycle of a pig this might result in direct infection of the conceptus as does the transplacental transmission of HC virus indirectly to fœtuses from a possibly subclinically infected sow. Naturally this latter mode of transmission occurs at any time of the ontogeny or intrauterine life and presents probably much more infectious virus to the fœtus than the sow ever received herself. The fœtus is even floating in amniotic fluid rich of virus. This needs mention for strengthening the quantitative aspect in relation to initiation of HC virus infections with or without the appearance of disease.

After embryos or fœtuses have been infected, they need to be considered as individuals as it applies to pigs infected postnatally. Any pathogenic event is primarily an embryonal or fœtal reaction, respectively, to the infecting virus thus initiating mechanisms different from the pathogenesis of hog cholera in mature pigs. HC virus has the potential to perfectly adapt to the type of host which offers susceptible cells at the site where primary contacts occur. The interactions triggered by the virus after multiplication at the primary site can be grouped according to their immunological or non-immunological nature. Former reports on the existence of HC virus strains of low or non-immunogenicity are still a matter of controversy and need reconsideration in the light of (i) antigenic strain variation (Neukirch et al 1980), (ii) growth characteristics "in vivo" and "in vitro" (Aynaud et al 1977) as well as (iii) deficiencies in immunologically immature pigs devoid of humoral immune response after postnatal contact with HC virus (Liess et al 1976).

Early in ontogeny no immunological reaction but rather inducement of immune tolerance by the virus is to be expected resulting in persistent infections frequently lasting beyond the term of delivery (Meyer 1978). Following infections at later stages of intrauterine life, some fœtuses may develop antibodies (Van Oirschot 1980). It may be argued that this phenomenon is not characteristic for the infecting virus and should be rather listed under "host factors".

2.2. Host factors

Of the host factors required for the initiation of HC virus infection as mentioned above, the porcine organism offers susceptible cells at the organ where under field conditions the virus enters the body by natural routes, that are the tonsils. In the tonsils, the epithelial cells on surface and in crypts appear to be the primary site of multiplication from where dissemination of virus by lymphocytes seems to occur via the corresponding lymphnodes into the circulating system.

Target cells for virus multiplication include (i) endothelial cells, (ii) lymphoreticular cells and macrophages, and (iii) epithelial cells. HC virus replicates in endothelial cells without apparent damage (Cheville and Mengeling 1969, Edwards *et al* 1984) and thus appears to behave in much a similar way as bovine viral diarrhea (BVD) virus in cattle.

Immunofluorescence studies have shown that HC virus has a distinct affinity to cells of the lymphoreticular organs with severe depletion of lymphocytes. The virus also multiplies in epithelial cells of many organs including submandibular salivary gland, mucosal cells of the small intestine and renal epithelial cells. The most intriguing organs in relation to vital systemic functions harmed by HC virus are apart from the vascular and lymphoreticular system the adrenals and the central nervous system.

2.3. Disease pattern

Infections with HC virus running clinically apparent courses can result in (i) acute or (ii) chronic disease, while inapparent (subclinical) infections in pregnant sows often cause severe damage to the fœtuses due to (iii) prenatal infections.

2.3.1. Acute disease

Once in the circulatory system, HC virus can gain access to all the cells lining the capillaries and lymphatic vessels with the opportunity to trigger mechanisms which eventually may result in clinical signs of some kind, eg, the highly impressive classical course of infection which earned the names hog cholera, swine fever or even classical swine fever (CSF). The characteristic lesions seen in the classical course of HC virus infection are those of haemorrhagic diathesis with petechial haemorrhages in most organ systems and serous membranes as reviewed by Trautwein (1986).

The severity of changes will be determined mainly by the virulence of the HC virus strain involved and the reactivity of the individual host as described above. In addition, it is known that secondary infections with bacteria may intensify and even modify the pathological picture. Therefore gnotobiotic piglets have been experimentally infected with HC virus and again showed the occurrence of petechial haemorrhages primarily in kidneys and lymph nodes (Weide *et al* 1962).

2.3.2. Chronic disease

A chronic course of HC virus infection has been defined by Mengeling and Cheville (1968) as lethal disease with a duration of 30 days or more. Since the clinical picture may often be uncharacteristic, the chronic disease was often refered to as "atypical swine fever" with little evidence of petechial haemorrhages. In the large intestine bouton ulcers are occasionally followed by a more diffuse diphteroid-necrotizing enteritis which compares with the term "hog cholera" as this type of disease was called in 1887 by Salmon (cited by Zschokke, 1896) and who considered this as a disease *sui generis*. However, in this chronic form secondary bacterial infections are frequently involved.

In the slow, protracted course of the disease, single organ systems may be affected including lung and CNS.

2.3.3. Effects due to prenatal infection

In the prenatal stage of life, the porcine organism is highly vulnerable by HC virus and may display abnormalities of various kinds when aborted or after delivery at normal term. Transplacental transmission following natural exposure of sows to field virus or vaccination with attenuated live virus may result in prenatal death, mummification, anasarca, ascites, a rather large spectrum of malformations, congenital tremors, perinatal death or fatal outcome later in life after viral persistence (Trautwein, 1986).

From the epidemiological point of view, congenital persistent HC virus infections with viraemia and permanent virus excretion are the most interesting courses especially in the absence of any clinical signs which may eventually become visible during the first month of life or later (Van Oirschot and Terpstra 1977). This includes the development of a runting-like syndrome with growth retardation, dermatitis etc with a marked atrophy of the thymus at necropsy. Lesions characteristic of hog cholera, particularly petechial haemorrhages, are not present. This underlines that pathomechanims are involved different from those responsible in postnatal infections.

Serological studies in pigs with congenital persistent viraemia showed that they were not capable of producing neutralizing antibodies against HC virus while the response to other viruses appeared to be not impaired (Meyer 1978, Van Oirschot 1980). Since virus-antibody complexes were not found in significant amounts while the lymphocyte response to phytohaemagglutinin was only slightly depressed, immunotolerance was suggested as result of experimental inoculation of sows at 65 days of gestation (Van Oirschot, 1980). In general agreement with these findings were results obtained from similar experiments with a so-called low-virulence strain of HC virus administered intranasally and thus close to the natural route of infection. Sows were infected at about days 40, 70, and 90 of gestation, respectively (Meyer *et al* 1981). The majority of newborn piglets born from sows infected at 40 and 70 days of gestation proved to be infected at birth. Most of them died within the first week *post partum*. It was interesting to see that not all piglets of the same litter were infected. Those

born uninfected got the opportunity to acquire the infection from infected litter mates after they were born (Hermanns *et al* 1981).

Several piglets born infected after their dams were inoculated as late as days 85-90 of gestation lived with persistent viraemia for up to eight weeks without developing neutralizing antibodies. These results together with observations on congenital infections in the field (Van Oirschot and Terpstra 1977) bear high significance for the epidemiology and control of hog cholera virus infection.

2.3.4. Possible pathomechanisms

From the foregoing rough outline of HC virus infections and their clinical and pathological symptomatology, some possible pathomechanisms arose (for review: Trautwein 1986):

a) *Blood coagulation disturbances*

Multiple defects of haemostasis with activation of the blood coagulation system possibly due to direct damage of lymphoid tissue, endothelial cells and epithelial cells of the gastro-intestinal tract occur (Heene *et al* 1971); consumption of platelets and certain coagulation factors (consumptive coagulopathy) results in intravascular coagulation with severe effect on the micro-circulation (microthrombi) and eventually appearance of petechial heamorrhages.

The pathomechanism of damage to endothelial cells which might result in plasma and erythrocyte diapedesis is not clear as yet. The endothelial cells appear not to be injured by the replicating virus since there were no changes detectable in the plasma level of plasma-factor VIII-related antigen which would indicate an injury of endothelial cells (Edwards *et al* 1984).

b) *Destruction of lymphocytes*

This applies to B-cell and thymus-dependent areas and may be due to a direct toxic effect of HC virus or it may be caused by enhanced release of glucocorticosteroids from the hyperplastic adrenal cortex.

c) *Perivascular accumulation of lymphocytes in brain and spinal cord*

The functional significance of the histological changes are not clear and also not whether the immunocytes are responsible as T cells for a cytotoxic effect on infected target cells in the CNS or as B-cells for local antibody formation.

d) *Thymus atrophy*

In chronic cases, thymus atrophy was observed indicating immunological implications on the T cell system (Cheville and Mengeling 1969).

e) *Interaction with fœtal development*

The various abnormalities observed when the developing fœtus is exposed to HC virus obviously corresponds with critical periods of gestation. This includes teratogenic effects which are in general the more severe the earlier the infection occurs.

Congenital tremor was attributed to cerebellar hypoplasia and hypomyelinogenesis (Harding *et al* 1966, Vannier *et al* 1981).

Stillbirth follows usually maternal infection during the last third of gestation with characteristic lesions, eg, petechial haemorrhages (Johnson *et al* 1974, Meyer *et al* 1981). Premature formation of germinal centers and proliferation of plasma cells in lymphnodes and tonsils together with the elevation of fœtal serum immunoglobulins point at a virus-induced stimulation of the immune-system which in turn may be related to immunopathological events (Benten *et al* 1980, Richter-Reichelm *et al* 1980).

Interactions of HC virus with the fœtal host organism resulting in immunotolerance are highly important for obvious reasons. The mechanism leading to this phenomenon is still awaiting clarification.

3. Epidemiology

3.1. Prevalence

Acute outbreaks of hog cholera must be regarded as indicators for otherwise clinically unnoticed infections of a certain epidemiologically significant proportion of herds in some countries. In such swine populations, the prevalence of infection with hog cholera virus may be demonstrated by random sampling and serological testing of sera derived from breeding herds (Liess *et al* 1975, 1976). Where systematic vaccination is used such testing is of less value than in countries with successful eradication of hog cholera where surveillance may be based on serology.

3.2. Incidence

The classical course of hog cholera virus infection is easy to recognize and counts for most of the statistical figures given in regional, national or supranational reports. In the complete absence of cases from countries where vaccination is prohibited and some kind of serological surveillance is adopted, statistical information is probably more reliable than in other countries where even imports of pigs are not prohibited and quarantine measures are not exercised. The prevalence of hog cholera with incidence of only sporadic cases should not be underestimated especially in countries with HC live virus vaccination.

3.3. Spread

3.3.1. Source of virus

Although there are reports on the susceptibility for HC virus of various animal species, domestic pigs seem to be the major source of virus after

multiplication in several organs and excretion by the nasal, oral and intestinal route at high titers of virus. Provided means of transmission are available, eg insect bites or iatrogenic, blood in its viraemic phase or from persistently infected pigs can serve as a highly potent source of virus. If such pigs are slaughtered offals and fluids if fed untreated to susceptible pigs can initiate outbreaks of HC. However, one of the most important reservoirs of HC virus is the infected pregnant sow («carrier sow» according to Huck, 1964). After primary infection by, eg, the oral route and viraemia such a sow transmits the virus transplacentally to the fœtuses while she develops immunity as discussed above (see pathogenesis: persistent infection). The effects on the fœtuses are variable depending on the stage of gestation. The multiple role of the sow as source is that (i) she sheds the virus with placental fluids and (ii) gives birth to infected fœtuses which form risks for pigs in nearby farms. In addition such sows (iii) can guarantee perpetuation of HC virus by persistently infected piglets which permanently excrete the virus and infect other pigs on transports to and in new herds.

3.3.2. Contact infection

Assumed that the virus contained in one of the sources mentioned comes into contact with susceptible pigs, it depends on the virus-host system whether infection takes place and disease occurs or whether merely antibody development can be demonstrated. Attempts to transmit by contact the HC virus strain «331» originally isolated from a chronic case by Cheville and Mengeling (1969) were unsuccessful (unpublished data). Neither the pigs (10) inoculated intranasally 3 days prior to the contacts nor the in-conctact pigs (10) showed any clinical signs. While the latter did not develop neutralizing antibody to any of the pestivirus strains tested (HC and BVD) the former did so with high titers against the homologous strain, lower to the heterologous HC virus strain and lowest or nil against the BVD virus strains used (NADL; A 1138/69). This indicates lack of transmission by contact for a strain of HC virus which is apostrophized as of low-virulence. On the other hand it may be questioned whether infection with strains of HC virus do necessarily result in excretion in such amounts as to infect other susceptible pigs by direct contact. Since strain «331» came from the USA before vaccination against hog cholera was abolished, it is tempting to ask whether it represents merely one of the vaccine strains used in the USA for long time before the eradication programme came into effect.

3.3.3. Economic involvements in epidemiology

Analysing data obtained from EEC member countries, Ellis et al (1977) described the disease situation and tried to explain the cyclical patterns of hog cholera outbreaks. The clearest evidence for a 3-4 year cycle was thought to exist since in many cases peaks in hog cholera incidence seemed to relate to peaks in pigmeat prices. According to Ellis et al (1977) the pigmeat price is a reflection of the changes in the structure of the pig population. Looking for further explanation of seasonal pattern of outbreaks defined as incidence of the disease, strong evidence was obtained on an association of breeding stock and piglet production with the pattern of disease incidence. Movement of pig has long been considered to contribute to more cases of hog cholera than any other known factor (Beals et al 1970). It would be difficult to understand why this does not apply to piglets in view of possible persistent infections as described in the above section on the pathogenesis.

4. Concluding remarks

The present paper does not substitute other comprehensive reviews on hog cholera, eg by Dunne (1973). However, it offered the opportunity for expressing some unorthodox views in relation to the pathogenesis and epidemiology which would have been impossible without some safe foundation on the numerous reports on this subject matter worldwide. Many gaps have still to be filled on a colourful map representing a virus infection which probably had its origin in the wildlife and turned out to be quite successful against attempts to industrialize pig production. Surely the story has not come to an end, yet.

Abstract

A review is given on the infection with hog cholera (HC) virus resulting in various courses due to variabilities of the virus and the porcine host organism. Mechanisms by which the virus causes prenatal death or postnatal disease in pigs are considered. Epidemiological features relating to various courses of infection and disease patterns resulting from prenatal or postnatal contacts with the virus are discussed.

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