

# Biological characteristics of the RHD (rabbit haemorrhagic disease) virus – novel data

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## Abstract

The paper presents the characteristic of RHDV virus determining the main threat to domestic and wild rabbits. It characterizes the RHDV entering to rabbit's organism way and describes pathogenesis of rabbits' plague as well as biological features that differ particular well known RHDV strains. There has been both immunogenicity among RHDV strains and their hematological reactivity described. There has been presented diagnostic methods of disease caused by RHDV – the germ that induces symptoms similar to viral hemorrhagic fever (VHF) viruses and viruses that are the reason human hepatitis.

**Key words:** rabbit, RHD virus, strains of RHD virus.

(Centr Eur J Immunol 2009; 34 (4): 261-270)

## Introduction

When in 1984, in China, Jiangsu Province, a new infectious disease was recorded that mortally attacked rabbits from the *Oryctolagus cuniculus* species [1], no scientist predicted such a fast spread of the disease, as presently it affects rabbits on all continents [quote in 2-4]. According to the recommendations of OIE (Office International des Epizooties), in 1989 [98], the disease previously referred to as Chinese haemorrhagic disease, lagomorph haemorrhagic disease, haemorrhagic bronchopneumonia, haemorrhagic septicaemia, hepatonecrosis, disease X, sudden viral rabbit death, rabbit haemorrhagic fever, was called viral haemorrhagic disease (VHD), although in Poland the former name is also used [quote in 3, 4]. In the meantime, the studies regarding the aetiological factor of the disease showed that it is the RHD (rabbit haemorrhagic disease) virus which, according to the present systematics [6], belongs to the *Caliciviridae* family, *Lagovirus* genus, which also includes non-pathogenic RCV (Rabbit Calicivirus) virus and pathogenic only to hares – the EBHS virus (European brown hare syndrome).

The RHD virus is sheathless, of 28-40 nm size and 1.310-1.365 g/cm<sup>3</sup> density. It occurs in the form of a regular

icosahedron with thirty-two capsomeres, containing single-stranded, linear, positively polarised RNA acid composed of 7437 pairs of alkalis. Most of the genome is covered by the large (ORF1) and small (ORF2) reading frame. ORF1 comprises 7034 nucleotides and encodes polyprotein of the 257 kDa size, which as a result of action on the part of viral proteases decomposes into 7 non-structural proteins, coded at 'terminal 5' of the frame, and structural capsid VP60, coded in terminal 3'. In turn, ORF2 comprises 353 nucleotides and encodes VP10 protein with molecular weight of 10 kDa, whose function has not been finally defined. It has been shown that the most important component of the virus is the VP60 protein with molecular weight of 60 kDa, which at the amine terminal contains the S domain protecting the genome, while at the carboxyl terminal – P2 domain containing two hypervariable regions C and E, among six differentiated in the protein, namely A, B, C, D, E, F, which (C and E regions) are the best place defining genetic variability of strains of the RHD virus [7-12].

## Biological characteristic of RHD virus

Among biological properties differentiating strains of the RHD virus, one must mention their general capacity for

erythrocyte haemagglutination (HA) in all human blood groups, although in the ca of routine studies, usually 0 group erythrocytes are used [10, 13, 14]. It must also be added that among the presently described strains of the RHD virus, seven of them do not show this property, namely: *English Rainham strain*, obtained by Central Veterinary Laboratory in Weybridge in 1993 from naturally deceased rabbits in southern England [15, 16], with which the hypothesis emerged that there is more than one source of infection of rabbits with the RHD virus and that the source may additionally come from hares in the United Kingdom, infected with the EBHS (European brown hare syndrom) [15, 16]; *Blaszki strain* – BLA, from rabbits bred in central Poland, deceased with syndromes typical of the VHD in the summer of 1994 and obtained from National Veterinary Institute in Puławy – Foot and Mouth Disease Department Zduńska Wola [17]; *Spanish Asturias strain* obtained from 2-6-month-old rabbits from north-western Spain in 1996 at Laboratorio de Sanidad Animal de Asturias in Gijon, where asymptomatic course of the disease was observed and 10% mortality, yet with typical of the RVHD anatomopathological lesions in the liver in the form of hepatocyte necrosis and necrotic foci in the trachea and lungs [18, 19]; *German Frankfurt strain* (Fra) obtained from the naturally deceased rabbit in 1996 from the area of Frankfurt by Friedrich-Loeffler-Institutes, Insel Riems [20, 21]; *Chinese whn-1 strain* obtained from rabbits with no information regarding the place of origin or year of obtaining, yet which reveals nucleotide homology at the level of 91.2% with the Rainham strain [22] and 98% homology with non-haemagglutinogenic antigen variant 99-05 of the RHD virus [22], as well as two *Italian strains*: *Pv97* – from rabbits that died in 1997 near Pavia (Italy), and *Bg97* – also coming from rabbits that died in 1997 in the regions near Brešci (Italy) [2, 21, 23]. There are also data [21] reporting that the German *Hartmannsdorf* strain, obtained in 1996 from dead rabbits, also does not show haemagglutination capacity, similarly as the described Polish *ŽD* strain [24] and German *Hagenow* strain [21], which remain at the border of haemagglutination capacity, as they react variably in the HA test. The Polish *ŽD* strain was obtained in 2000 from naturally dead rabbits, which after single passage showed haemagglutination capacity and was marked as *ŽD1* [24]. In turn, the German *Hagenow* strain is characterised with negative or very low titre in the HA test, also obtained from naturally infected rabbits in 1990 [21], and similarly as *ŽD1* strain recovers the haemagglutination capacity after a single passage [2, 21]. Furthermore, Capucci et al. [23] reported that the aforementioned Italian *Bg97* strain of the RHD virus, described as a non-haemagglutinogenic strain, also reveals haemagglutination capacity, but only at the temperature of 4°C and pH 6.8 or lower.

Another important biological property of the RHDV strains, of which approx. 400 (hypotetically) have been studied, is the differentiation among them of 27 so-called antigen variants marked with symbol RHDVa. These are

strains coming from: *Italy* – *Pavia 97 (Pv97) and Viterbo97 (Vt97) strains* [25], *Germany* – *Triptis and Hartmannsdorf strains* [21], *France* – *9905RHDVa, 03-24 i 00-Reu strains* [26], *USA* – *Iowa 2000-IA00, UT01, IN05 i NY01 strains* [27], *Hungary* – *RH29/03 strain* [28], *Cuba* – *CUB5-04 strain* [29], *China* – *WHN1* [22, 27], *WHN2, WHNRH, WHN-ZTP, CD, NJ1985, JXCHA97, YL* [27], *the Netherlands* – *NL2004-1, NL2004-2, NL2004-3* [30] and *Poland* – *L145/04 and W147/05 strains* [31]. They have a characteristic structure of the hypervariable region E of the VP60 protein (this region features antigen determinant for the 1H8 antibody) and a different capacity for adherence to the monoclonal antibodies 1H8 and 6G2, 6H6, or specific way of reacting with the 3B12 antibody. They belong to the G6 genogroup of the RHDV, which is similar to the G1 genogroup, which includes the so-called ‘old’ (classic) strains of the RHDV, obtained from sick and dead rabbits due to VHD in the years 1984-1989, which would point to the origination of the variants due to the reaction of classic (‘old’) strains with the ‘new’ strains, including from vaccines, of the RHD virus [8, 21, 22, 25, 26, 32, 33]. It is assumed that they are characterised with high maliciousness, which feature differentiates them from the non-pathogenic Rabbit Calicivirus RCV, and which would form evidence to exclude the possibility of their origination as a result of recombination of the RHD and RCV viruses [26, 28].

Further important biological properties of the RHD virus strains is their difference in the area of pathogenicity (although not very precisely described, as no pathotypes have been differentiated for this virus), genetic difference, serological and immunological difference, and their creation of a varied haematological image, and their inclusion of apoptosis in many cells, and causing changes to biochemical factors.

And so, pathogenicity of actually all the strains of the RHD virus so far recorded in the literature, assessed via the animal mortality percentage, has differentiated very pathogenic strains, rendering rabbit mortality of from 70% to 100%, and weakly pathogenic strains causing mortality of up to 25-30% [quote in 3, 4, 34].

In turn, genetic studies of over 400 RHD strains, including the strains obtained from the first foci of RHD among naturally infected rabbits, have pointed to differences between them, in particular between European strains and British strains, ranging from 1.0 to 14%, which has allowed for their grouping into 8 genetic groups (G1-G8) [20, 26, 35, 36 and quote in 2, 3, 31]. Moreover, studies in this respect regarding this virus (37) have led to learning the full nucleotide sequence of 32 strains of the RHDV and learning the full sequence of the genome encoding the structural VP60 protein in 37 strains of the virus, as well to describing in a proximally 300 strains of their fragmentary sequence of the gene encoding the VP60 protein and genes encoding other proteins.

As regards the property of the RHD virus related to its serological response, it must be stated that it was only performed for 4 strains coming from Italy, Spain, Korea

and Mexico [32], where a different reaction was only recorded for the strain from Mexico to five monoclonal antibodies (3H2, 3H6, 5D1, 6G2, 1H8) [32].

### **Immunogenicity of the RHDV strains**

In turn, the analysis of the immunogenicity of the RHD virus strains was performed by assessment of the immunological reaction in rabbits only experimentally infected with this virus in China [1, 7, 38-44] and Poland [3, 4, 34, 45-77, 79-101, 141]. The studies of the Chinese authors [1, 7, 38-44] referred to just 5-7 immunity factors in rabbits infected with 5 Chinese strains of the RHDV, while Polish studies [3, 4, 34, 45-101] referred to infection with 16 strains of the RHD virus originating from France, the Czech Republic and Poland, and rabbits where (although not always) 15-20 factors of non-specific and specific, cellular and humoral immunity were assessed. It must also be added that the studies by Chinese authors were generally performed in the static system, without differentiation of the strains studied. In turn, Polish studies regarding 16 strains, performed in the dynamic system, revealed their different reaction in the immune system of rabbits, which suggests the occurrence of immunotypes among the RHD virus.

The study of haematological reactivity of the RHD virus was assessed in rabbits in the scope of 7 haematological parameters, infecting rabbits with 19 strains of the RHD virus originating from China, Austria, Israel, Italy, Germany, Korea, Spain, France, the Czech Republic, and Poland [3, 4, 34, 38, 43, 48, 49, 90, 102-115 and quote in 65, 116], which, despite causing differences in the values of parameters defined in the animals studied, did not group them as in the case of immunological studies. It must also be added that within haematological studies, also the thrombin time and prothrombin time in rabbits infected with not strictly defined Chinese strains of the RHD virus (no number and name defined) [38, 102, 103, 114, 115], as well as in rabbits living in the wild [107] with unnamed 3 Austrian strains, and in domestic rabbits [106, 110], with also unnamed strains of the virus from England and Poland, which also did not group the strains studied. The studies performed [77, 117-119 and quote in 120] regarding the assessment of RHD virus impact on apoptosis, did not differentiate the strains assessed. This phenomenon was initially described with histological methods in many cells of the macroorganism, including macrophages and eosinophils in rabbits infected with unspecified strain of the RHDV [117, 118]. Further studies of apoptosis were performed by caspase activation [77, 119], recording the stimulating or suppressive impact of the virus on the process of apoptosis [77] in rabbits infected with the Spanish strain AST/89 and two Italian strains Pv97 and Vt97.

Also the assessment of the image of changes to biochemical factors (liver aminotransferases, bilirubin, creatinin, urea, and  $\gamma$ -glutamyltransferase) in rabbits infected with one Spanish strain [104, 105, 121-124], two Polish strains

[106, 125, 126], and two French strains [126], as well as one Austrian strain [107, 110], did not reveal, just as in the case of apoptosis, a different impact of the strains studied on the parameters assessed.

### **RHD virus characteristic**

The hosts for the RHD virus can only include domestic rabbits of meat breeds and angora, and mix-breed, as well as wild rabbits, mainly adult individuals [quote in 2-4, 127], although the results from recent years [18, 128-132] have revealed that the RHD virus breaks the barrier of maternal immunity in young rabbits, already causing in 2-4-week-old animals [128-131], lesions typical of RHD in their internal organs – without causing their death. Also Prieto et al. [18] revealed in 3-6-week-old rabbits naturally infected with RHDV, in post-mortem studies, the infection of liver tissue with high infiltration of MN (macrophages and monocytes) cells and hepatocyte necrosis (image similar to lesions observed for hepatitis in humans), despite no record of histopathological lesions for RHD in the liver, spleen, kidneys, thymus, lungs, intestines, heart and brain (except for one rabbit). The thesis of susceptibility of young rabbits to infection with the RHD virus was also presented by Cooke et al. [133], in 4-10-day-old rabbits for whom the presence of the microbe was recorded in the liver after 12-72 h from their contact with RHDV. Also Shien et al. [132], using the RT-PCR method, in 4-5-week-old rabbits infected with the RHDV, recorded the presence of the viral RNA in the liver and bile, and in the spleen and mesenteric lymph nodes. In such animals, also the increased internal body temperature was observed, prevailing for 5-7 days, which then decreased, probably – as the author says – due to the occurrence of the anti-RHDV antibodies in serum of such animals [132]). Mikami [130] explains that the sensitivity of young rabbits to the infection with the RHD virus depends on the development of some undefined hepatocyte membrane component, the presence of which is only recorded in some young rabbits. According to Ruvoën-Clouet et al. [131], young rabbits' susceptibility to infection with the RHD virus is conditioned with the virus capacity to adhere to the receptors of the ABH blood group, the presence of which in the animals was revealed on epithelial cells of the digestive and respiratory system.

While presenting the RHDV, it is worth adding information about the potential possibility of infecting other animals with it. The studies have only revealed the occurrence of antibodies for such a microbe in dogs, red foxes, cats and mice, although it was also stated that many species of domestic animals (authors did not specify the species) show lack of sensitivity to the infection with this virus [134]. Also, temporary appearance of specific serum anti-RHDV antibodies in the HA test has been described in experimentally infected swines [135]. Such specific antibodies were not found in serum of people having

contact with RHDV [136]. In turn, in cats infected by eating the liver of rabbits sick with RHD, after 10 days, antibodies to the RHD virus have been found in blood serum, and the virus was detected in lymph nodes of the intestines, tonsils, spleen, and liver, whereas cats did not show any symptoms of the disease [137].

What must also be mentioned, is the occurrence in rabbits that had no prior contact with the RHD virus, of anti-RHDV antibodies, termed as natural [138 and quote in 3, 4, 46, 90], which antibodies – as it is assumed nowadays – are principally synthesised by lymphocyte B1 [139] or probably occur after stimulation of such animals with non-pathogenic RCV virus that shows 91.5% similarity with RHDV in the capsid protein aminoacid sequence [31]. There are recent reports [140] of the occurrence of another non-pathogenic strain of the RHDV, obtained from serums of healthy rabbits living in the wild on Lambay Island near Dublin, where the presence of antibodies for the RHDV has been detected. There is evidence that the strain causes latent infection in rabbits and is in 81% similar in the genetic aspect to the RCV virus. One must also mention the EBHS virus, also belonging to the Caliciviridae family and the Lagovirus genus, to which the RHDV belongs, and which – as it is assumed – is only pathogenic to rabbits, although its similarity to the RHD virus is at the level of 76.4% [31], and it is possible that this is the reason for the present [78, 141] reports of asymptomatic infection in rabbits after experimental, intramuscular administration of the EBHS virus.

### **Penetrates routes and pathogenic action of the RHD virus**

In the natural conditions, the RHD virus penetrates rabbit organisms via the aerogenic, alimentary route, and through the damaged body tissues, while in experimental conditions animals can be infected intramuscularly, subcutaneously, intraperitoneally, intravascularly, and intraconjunctivally [quote in 3, 4]. The resulting disease has the hyperacute course (rabbit mortality usually amounts to 100%), acute course (mortality in the range of 80-90%), and hypoaacute course (mortality of approx. 40-60%) [quote in 3, 4]. So far, although the data were presented before 1992 (quote in 142), it is assumed that the mechanism of RHDV's impact on the rabbit organism is related to the affinity of the virus to blood vessels, where it causes damage to endothelium and disseminated intravascular coagulations. This leads to extravasations and haemorrhages typical of the disseminated intravascular clotting, so called DIC syndrome, mainly in the liver [quote in 3, 4, 90, 142]. According to Keşy et al. [106] and Tunon et al. [143], the aforementioned lesions explaining the pathogenic action of the virus, may form evidence that the image of the rabbit infection with the RHDV may be specific to learning the pathogenesis of the VHF in humans, causing lesions typical of the DIC syndrome, acute course of the disease and

high mortality – properties typical of the RHD, whereas morphological lesions are principally recorded in the liver [quote in 3, 4, 142, 144], analogically as the lesions occurring in viral hepatitis in humans (143). It was also proven [104, 122, 130, 145] that in rabbits infected with the RHD virus, apart from the previously described morphological lesions (in the liver, lungs, spleen, central nervous system and heart), high aggregation of granulocytes, lymphocytes and macrophages is recorded in the liver. When studying the pathogenesis of the RHD in 4-10-week-old rabbits and adult animals, it was shown that during their experimental infection with the RHD virus, analogically as in the case of viral hepatitis in humans, increased activity of liver enzymes is observed already at 36h from infection with the virus, as well as decreased level of clotting factors, e.g. of factor VII, and glutathione oxidase [104-107, 110, 121, 123, 125, 126]. Furthermore, Keşy et al. [106] proved in rabbits experimentally infected with the RHD virus not only increase in the AspAT activity, but also increased creatinine concentration, pointing to renal lesions. Moreover, in rabbits infected with the RHDV, decreased activity of superoxide dismutase was detected in liver cells, but there were no changes to mRNA which conditions the synthesis of TNF- $\alpha$ , as well as TGF- $\alpha$  and TGF- $\beta_1$  [124]. The same authors [124] state that in these animals, in liver cells, the nuclear factor  $\kappa$ B is activated, and nitrogen oxide (NO) synthesis is increased – causing pathological lesions recorded in hepatocytes. Another testimony to the impact of the RHD virus onto the liver tissue in rabbits after infection with the RHDV is the apoptosis of the cells of this organ, evidenced with histopathological methods in rabbits infected with the RHDV (unspecified strain), not only in hepatocytes, but also in epithelial cells, and cells of the lungs, kidneys, heart, spleen, lymph nodes and in peritoneal macrophages and eosinophils [117, 118]. This phenomenon was also observed in hepatocytes of rabbits infected with the Spanish RHDV – AST/89 with caspase 3 activity at 36 and 48 h from infection [119]. In turn, the study by Deptuła et al. [77] evidenced in hepatocytes the inclusion of apoptosis, determined by activity of caspase 1,3,4,5,6,7,8,9 already from hour 4 from infection of rabbits with the Italian Pv97, Vt97 of the RHD virus.

It must be added that the aforementioned facts enriching the data regarding the RHD virus, not only in the aspect of its impact on the immune system cells [2, 4, 34, 47, 49, 51, 55, 58, 60, 62, 64, 65, 67, 71, 77, 80, 82-84, 88-90, 97-100, 146-149], or the phenomenon of apoptosis [77, 117-119] in rabbits infected with the RHDV, linked with the image of lesions in the liver [104-107, 110, 121-126], still do not fully explain the pathogenesis of the RHDV and the 'path' of the pathogenic action of the RHDV. Although immunological studies prove and indicate that mainly the factors of non-specific cellular immunity, but also the parameters of non-specific humoral immunity and specific cellular immunity form important elements that probably impact on the course of the disease and the pace of dying, which was testified with

the increase and decrease of factors assessing such immunities during the infection and just before the death of animals, yet extension of such particular studies is necessary as it is still difficult to clearly define that these are fundamental elements in the pathogenesis of the RHD virus.

## Diagnosics VHD

When presenting the characteristics of the RHD virus, it must be stated that the diagnostics of the disease caused by this microbe is practically based principally on the clinical image, anatomopathological lesions of the internal organs (principally the liver), serological tests (haemagglutination test – HA, ELISA test min. with the use of monoclonal antibodies), and virusological studies (immunofluorescence and electron microscopy), and recently it has partly been extended by studies using molecular biology techniques [2, 150 and quote in 3, 4, 90]. In turn, when preventing the RHDV, the inactivated organ vaccine is still used, where the source of the antigen is the liver of infected rabbits [quote in 3], as so far, apart from the reports by Chinese authors [40, 151], the virus has not been multiplied in any of the known cell culture systems. There have been recent attempts [quote in 3] to produce a vaccine containing the so-called virus like particles (VLP) [2, 31, 152 and quote in 3], or vaccines based on very immunogenic strains of the RHDV [90]. There are also attempts to construct a recombinant vaccine based on capsid protein VP60 of the RHD virus, in many hosts, including *Saccharomyces cerevisiae*, *Pichia pastoris* [153, 154], or recombinant animal viruses [155, 156]. Also, a new path is searched to obtain the VP60 protein of the virus, in transgenic plants (potatoes with the expression of recombinant VP60 protein), which can be used for oral immunisation of farm rabbits and rabbits living in the wild [116, 146, 157].

Therefore, one may say that despite the lapse of many years from the occurrence of this pathogenic agent (RHDV) in the environment and its generally established taxonomic position, there are still many unexplained issues, principally as regards the biology of the virus, like in the area of searching for and evidencing the immunotypes, presenting the course of pathogenic action of the RHDV on the rabbit organism and its pathogenesis, which additionally, in the context of very similar or analogical recorded lesions caused by viruses causing viral haemorrhagic fevers (VHF) in humans, and partly viruses causing hepatitis in humans, principally as regards lesions in the liver, presents the RHD virus as a very interesting field of study for scientists.

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