

LENTIVIRUS INFECTIONS OF UNGULATES.
III. PATHOGENESIS & SYMPTOMS

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Summary

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In this part of the review author describes the pathogenesis, pathomorphology & symptoms of diseases caused by 5 lentiviruses.

Key words: lentiviruses, pathogenesis, symptomatology

The term “slow infection” was introduced for the first time by the Icelandic researcher B. Sigurdsson in 1954 (Sigurdsson, 1954). With this term, he designated the interaction of the virus with the host, characterized by a prolonged (many months and even years) incubation period, at what time several organs or systems become affected and thereafter, results in slow, but progressive development of symptoms of the disease and an inevitable death. Fifty years later, the agents of classical slow infections (the maedi-visna virus, the caprine arthritis-encephalitis virus, the feline, simian and human immunodeficiency viruses) were put together with other phylogenetically related retroviruses (the equine infectious anaemia virus, the bovine immunodeficiency virus and the Jembrana disease virus) in the Lentivirinae family.

Not all lentiviruses correspond to the criteria of Sigurdsson. The Jembrana disease for instance is characterized with acute course, the equine infectious anaemia (EIA) occurs both acutely and chronically, maedi-visna (MV) in sheep and

caprine arthritis encephalitis (CAE) are classical slow infections and as to the persistent bovine immunodeficiency (BI) infections, by recently it is not known if it has a clinical stage. In the process of evolutionary divergence, lentiviruses (LV) have preserved some common traits and acquired new ones, conditioning clinico-pathomorphological variations of their interaction with host's organism.

MECHANISM OF LV PERSISTENCE

The principal target cells for LV *in vivo* are monocytes/macrophages and lymphocytes. After penetrating into the organism, LV reproduce in lymph nodes, the spleen and the bone marrow that become a kind of pool, from which monocytes and macrophages deliver the provirus in the entire organism. After getting into the brain, lungs, joints and other organs, monocytes mature, transform into macrophages and thus create preconditions for activation of the provirus and initiation of productive infection. Such a route of dissemination of the infection is highly reli-

able, because infected immunocompetent cells serve as Trojan horses: the viruses within them are not recognized by the immune system and thus, remain intact. The persistence in these cellular elements is one of the primary pathogenetic mechanisms of the multimonth or multiyear lentiviral infection.

Another way for avoiding the factors of immunity is the genetic variability of LV. The most variable is the external glycoprotein of virions. The relation of the appearance of new variants of the agent in the organism of infected animals with the exacerbation of infection could be best followed out in EIA (recurrent viraemia, fever and other symptoms) (Kono *et al.*, 1973). The manifestation of the genetic mutability of MV, CAE and BI viruses are less obvious. In these infections however, the genetic mutations of agents do not occur less frequently than in EIA viruses (Cheevers *et al.*, 1991). It was found out that in the organism of immunocompetent sheep, several genetically different variants of the MV virus, deriving from the original strain, could persist at a time (Clements *et al.*, 1988). It was already mentioned (Schuljak, 2006) that glycoproteins of LV envelope are responsible for the choice of target cells and the penetration of the agent within them, and after that, for its transmission from cell to cell. The alterations in the structure and properties of this protein are inevitably resulting in the emergence of agent's variants with biological properties, differing from those of the parental strain (taking into consideration the pathogenetic role of glycoproteins in the provision of tropism and virulence). After all, the infected animals become a source of numerous variants of the agents. Such a heterogeneous quasi-strain possesses an increased "floatage" – depending on occurring conditions

(immune response etc.), some LV variants die or could not actively reproduce whereas others receive a "green light" (Lairmore *et al.*, 1988).

The most important path of the evolutionary divergence of LV is the adaptation to the different cells of the immune system. The EIA, MV and CAE viruses are able to reproduce in macrophages and at a lesser extent – in other somatic cells. Finally, the degree of permissibility of these LV to mentioned cell elements determined the type of caused infections.

The BI virus became accustomed to reproduction within macrophages and lymphocytes. It shows a tropism not only to CD4 lymphocytes as the human or simian immunodeficiency viruses, but also to CD3, CD8+, $\gamma\delta$ -T- and B-lymphocytes (Wu *et al.*, 2003). Yet, very little is known about bovine immunodeficiency, including its pathomorphological and clinical manifestations. The pathogenesis of LV infections from the first group is far better known. The reproduction of these agents in tissues is accompanied by an intensive inflammation manifested with macrophageal lymphocytic infiltration and formation of lymphoid follicles. At the end, perivascular infiltrates do appear in organs and an interstitial inflammation is developing.

CLINICAL AND PATHOMORPHOLOGICAL FEATURES OF LV INFECTIONS

EIA. The duration of EIA incubation period, the possibility for evolution of the infection into the clinical stage as well as the character of the disease are primarily dependent on 2 factors: the immune status of susceptible animals and the virulence of the infective strain.

When the infection is introduced in infection-free farms, single animals become

sick in the beginning and after several weeks, the incidence of disease increases significantly.

In infected farms the acute form of EIA develops as a rule only in newly coming horses, whereas in the others it follows a chronic pattern.

The strains with low virulence cause asymptomatic infections or a mild disease after a long incubation period (Sellon *et al.*, 1994).

The incubation period of infections, caused by highly virulent strains, lasts for 2–6 weeks. The first attack of the disease occurs at the peak of viraemia (10^7 – 10^8 virions/mL) and is accompanied by fever (39.5–42 °C), depression, anorexia, haemorrhagic diathesis, as well as thrombocytopenia (< 150 G/L) and anaemia. There is a positive correlation between the severity of viraemia and these blood alterations. The most distinctive sign of the disease is thrombocytopenia. It develops secondary to the virus-induced damage of vascular endothelium (Oaks *et al.*, 1999), destruction of thrombocytes by immune factors and cytokines and also, the impaired maturation of megakaryocytes (Thornquist *et al.*, 1997). The most potent inhibitors of the megakaryocytopoiesis are the tissue necrotic factor- α , the transforming growth factor- β and α -interferon, that are intensively produced by macrophages in periods of recurrence of the disease. The haemolytic anaemia is considered as a consequence of haemorrhagic diathesis and erythrophagocytosis, associated with activation of the C3 component of complement.

Acute episodes of the disease could be very severe and end lethally within 3–5 days. Yet, frequently the first episode becomes limited for some weeks and the infection acquires a chronic course, alternating periods of aggravation of symp-

toms with periods of remission, when infected animals appear clinically healthy. As a rule, the severity of recurrence decreases with time with increasing the intervals between episodes. Having suffered the first attack of the disease, the organism of ungulates begins to control the reproduction of the virus via cytotoxic CD8+ lymphocytes and specific neutralization antibodies (Perryman *et al.*, 1988).

The progression of the disease is usually accompanied by infiltration of the liver, kidneys, spleen and lungs with mononuclear cells (McGuire *et al.*, 1971) as well as by intensive reaction of the reticuloendothelial system. This triggers further clinical signs caused by the inflammation of these organs (hepatitis, glomerulonephritis etc.) and impaired metabolism (for instance, the icteritiousness in EIA is resulting from impaired metabolism of haemoglobin).

Rarely, EIA is manifested in a nervous form without fever and the typical blood alterations (McIlwraith & Kitchen, 1978).

The intensity of viraemia and blood changes are gradually decreasing. The administration of immunodepressants (corticosteroids) usually results in worsening of the asymptomatic infection. The prolonged persistence of high blood serum titres of specific antibodies and the possibility of infection of susceptible to this infection ponies (Coggins, 1984) are evidence that many horse having suffered one or several episodes of the disease, remain persistently infected.

Maedi-visna. Maedi (progressive pneumonia) is the commonest clinical manifestation of MV infection. In affected sheep, dyspnea appears only when a considerable part of lungs are diffusely infiltrated with inflammatory cells. Initially, it is noted when the animal is moving, and then, becomes apparent in the state of rest

too. Together with hyperplastic interalveolar septae, infiltrates form germinative centres. The usual interval from the instant of infection to the appearance of lymphoproliferative interstitial pneumoniae is about 1.5 years or more. In the clinical stage of the infection, apart the dyspnea, a progressive weight loss is also noticed, although the appetite of animals remains unaltered. The affected sheep die within 3–12 months (Marsh, 1923). The complication-free course of maedi is characterized with lack of fever or other clinical alterations. The secondary bacterial and viral infections determine the actual symptoms. In particular, the simultaneous course of maedi and adenomatosis of lungs is frequently accompanied by repeated and profuse serous-watery nasal secretion.

The visna affects animals aged 1 year and older. During the long incubation period, in their central nervous system, a multifocal non-purulent encephalitis accompanied by astrocytic gliosis and demyelination is developing (Petursson *et al.*, 1976). Leukoencephalomyelitis could spread in the grey substance of the brain and spinal cord, but neurons are not destroyed. A long time prior to the onset of the first neurological disturbances, the concentration of cells in the cerebrospinal fluid is increased. The pleocytosis of the liquor is maintained during the entire course of the disease and serves as indicator of the intensity of CNS lesions (Petursson *et al.*, 1976).

Clinically, visna is manifested with ataxia, paresis and paralysis of hindlimbs. The affected sheep in the flock could be identified by producing a loud noise or using another irritant, able to frighten sheep and make them move in a hurry: the sick sheep remain behind, fall in lateral recumbency, still continuing to move their

legs as if running and making unsuccessful attempts to stand up. The interval between the appearance of the first clinical signs to the lethal issue is several weeks or months, when the symptoms advance. During a long visna illness, the fatness of sheep is considerably reduced.

The MV infection could be also accompanied by arthritis (Cutlip *et al.*, 1985), interstitial mastitis (van der Molen *et al.*, 1985), orchitis (Palfi *et al.*, 1989) and vasculitis of joint capsules, kidneys, the brain and meninges, lungs and trachea (Cutlip *et al.*, 1985). Yet, these manifestation often remain unnoticed or are attributed to other causes. Nevertheless, they are encountered very frequently and have a considerable economical impact. For example, at present the progressive pneumonia is rarely observed in many MV-infected farms in the Netherlands, whereas the interstitial mastitis is highly prevalent and is causing a decreased milk production of sheep and stunted growth of lambs (van der Molen *et al.*, 1985).

Blood alterations in sheep affected by MV are not observed, with the exception of increased immunoglobulin concentrations and the lower ratio of immunoglobulins and albumins (Karavaev *et al.*, 1983).

CAE. The clinical forms of CAE are several. The neurological form is very similar to previously commented disease but in goat kids, it appears earlier than visna in sheep – in the first 6 months of life.

Many goat kids die and in survivors, after 1.5 years or more, non-purulent arthritis, accompanied by subsynovial lymphocytic, macrophageal and plasmocytic infiltrations develop. The capsule of affected joints are distended by the excessive amount of synovial fluid. During the development of the disease, the cartilage is ulcerated and the subchondral surface

of bones is damaged. However, the arthritic form of the infection could affect adult goats that did not manifest neurological signs earlier in life (Crawford *et al.*, 1980). In this infection, the incidence of arthritis was significantly higher than that of the neurological form. In some goats, the arthritis is rapidly progressing, resulting in death but the cases where the disease becomes chronic, are not rare. The tarsal joints are most commonly and most severely affected, and at a lesser extent: the metatarsophalangeal, knee and atlanto-occipital joints. The radiography of affected joints showed an oedema of periarticular soft tissues, mineralization, osteoporosis, deformations (in old cases). The joint changes are so grave that often, they result in distensions and destruction of the locomotor apparatus.

CAE could also be manifested with interstitial pneumonia (Oliver *et al.*, 1982) and mastitis (Kennedy-Stoskopf *et al.*, 1985; Soesanto *et al.*, 1990).

The pathogenesis of CAE and MV in sheep are similar.

Jembrana disease. In Banteng cattle (domesticated Indonesian cattle), the first symptoms of the disease appear after a short (5–12 days) incubation period. The duration of the acute stage of the disease could be 12 days. In diseased animals, fever, somnolence, decreased appetite, enlarged surface lymph nodes could emerge. The mortality rate reaches 17% (Soesanto *et al.*, 1990).

In the acute stage of the disease, a number of haematological changes are observed: leukopenia due to lymphopenia, eosinopenia and neutropenia, thrombocytopenia, anemia, increased blood urea and reduced total blood protein levels (Soesanto *et al.*, 1990). The dissection of animals dead at this stage of the disease, a lymphadenopathy, enlarged spleen as well

as exudative and haemorrhagic alterations in tissues resulting from vascular wall damage, are found out.

Afterwards, in the organism of the affected cattle, an intensive lymphoproliferative reaction in parafollicular zones of lymph nodes and the spleen begins, seen also in other organs (especially the liver and the kidneys). Pulmonary infiltrations contain numerous macrophages. At the same time, atrophy of follicles in lymph nodes and spleen is distinguished (Dharma *et al.*, 1991).

Bovine immunodeficiency. The BI virus was isolated for the first time in 1972 from a 8-year old cow in Louisiana (USA), suffering from persistent lymphocytosis, neuropathy and progressive emaciation.

In calves, experimentally infected with this agent, the subcutaneous lymph nodes become enlarged without any other symptoms (van der Maaten *et al.*, 1972). The next reports about the fact that the BI virus caused the same alterations in immunity as human and feline immunodeficiency viruses, should be revised because the R29 strain, isolated by van der Maaten *et al.* and used in all trials with experimental infections of animals, was contaminated with the noncytopathogenic virus of bovine diarrhoea. Furthermore, it was shown that this BI isolate, similarly to other LV, has partially lost its virulence throughout the passages in cell cultures (Suarez *et al.*, 1993).

In Venezuela, a bovine paraplegic syndrome was reported – a lethal disease, where ataxia, hypoalgesia and paralysis of hindlegs at the background of leukocytosis, lymphocytopenia and monocytopenia were developing. In the course of 3–4 days after the animals could not stand up on their feet, death was imminently following. The incidence of immunoblotting

detection of antibodies against BI in the sera of animals from affected farms, varies from 12% to 66%. In rabbits infected with tissue extracts from sick cows, a seroconversion against BI antigens and appearance of the latter in tissues was observed (Walder *et al.*, 1995).

It could be assumed that the incubation period of the BI could be very prolonged and in most reports, the age of animals infected with the BI virus did not exceed 28 months. An exception are the first reports about the discovering of the agent and 2 publications with totally contradictory conclusions. In 1997, K. P. Flaming and his co-operates reported that throughout 4 years after experimental infection of calves with BI virus, there were no specific clinical alterations or a lethal issue in any of cases. The simultaneous inoculation of animals with BI virus and the bovine leukosis virus had not influenced significantly the development of both infections (Flaming *et al.*, 1997). At that time, the 5-year period of observation on 50 animals, naturally infected with BI virus in one dairy herd from the USA has been completed (Snider *et al.*, 2003). In cows infected with BI virus, a progressive weight loss, depression of the lymphoid system and impaired behaviour, characteristic for meningoencephalitis, have been observed. At the background of suppressed immunity, secondary infections developed that had an impact upon the clinical status of the animals. In the lymph nodes hyperplasia and dysplasia were shown. There was atrophy of lymphoid cells combined with lymphocytic depletion and folliculitis. By PCR, the provirus of the agent was detected in the foci of central nervous system and lymphoid tissue lesions (Snider *et al.*, 2003).

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Lentivirus infections of ungulates. III. Pathogenesis & symptoms

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