

DISEASES BY RETROVIRUSES

Oncoviruses (RNA tumour viruses)

(Sub-family: Oncovirinae)

Type C Oncovirus Group (most are exogenous)

Feline leukaemia virus

Feline sArcoma virus

Bovine leukaemia virus

Ovine leukaemia virus

Porcine leukaemia virus

Human T cell leukaemia virus

Avian type C Oncoviruses

Avian leukosis/sarcoma viruses (ALSV)

Reticuloendotheliosis virus

Lymphoproliferative disease of turkey virus

Type B Oncovirus group (endogenous)

Mouse mammary tumour virus (endogenous) (mammary-tumour milk virus)

Type D Oncovirus group (exogenous)

Jaagsiekte virus (pulmonary adenocarcinoma virus of sheep)

Lentiviruses (exogenous)

(Sub-family: Lentivirinae)

Visna / maedi virus

Caprine arthritis-encephalitis virus (CAEV)

Equine infectious anaemia virus

Feline immunodeficiency virus

Bovine immunodeficiency virus

Human immunodeficiency virus (HIV-I, HIV-2)

Simian immunodeficiency virus

Spumaviruses (foamy viruses, inapparent infections)

(Sub-family: Spumavirinae)

Bovine syncytial virus

Feline syncytial virus

Retroviridae is so named because these viruses contain the enzyme reverse transcriptase, an RNA-dependent DNA-polymerase (L. retro = reverse), which is carried in the virion of all retroviruses.

The proviral DNA of certain retroviruses is integrated in germ cells and transmitted vertically ("genetic transmission") with every cell thus containing proviral DNA. These viruses are known as "**ENDOGENOUS**", and usually remain quiescent (quiet, inactive). That is, they are not expressed, and are of low or no pathogenicity.

Viruses transmitted by the horizontal route are termed "**EXOGENOUS**", and are the most important retroviruses as causes of disease.

Retroviruses typically cause a **Chronic Cellular Infection** that does not lead to early cell lysis. In fact, with the oncoviruses, infection leads to **uncontrolled cellular proliferation**. This is in contrast to most other RNA viruses, in which infection and replication lead to **cell death**

Important Diseases caused by Type D Oncovirus group (Exogenous)

Jaagsiekte

(Common names, ovine pulmonary adenoma, ovine pulmonary adenomatosis (OPA), and pulmonary adenocarcinoma of sheep; driving sickness)

A tumour forming disease caused by type-D Oncoviruses, of the retrovirus family. Also called JSRV – jaagsiekte sheep retroviruses

Spread: The natural mode of transmission is by the respiratory route, probably via aerosols or droplets droplet infection from respiratory secretions, which are copious in sheep with clinical disease or even from

Pathogenesis: The virus replicates in the type II pneumocytes in the alveolus. Type II pneumocytes and Clara cells in the terminal bronchioles are transformed, and their growth produces intra-alveolar and intra-bronchiolar polypoid in-growths. These cells are surfactant-producing secretory cells, and there is also copious production of fluid. The excessive surfactant-like protein produced (in the tumour), provides a stimulus for the accumulation of macrophages, seen in this disease. The adenomatous in-growths of alveolar epithelium encroach gradually upon alveolar space so that **Anoxic Anoxia** occurs.

Signs

The incubation period in natural cases is 1-3 years. Clinical disease is rare in sheep younger than 2 years, and **is most common at 3-4 years of age**. The disease runs a **progressive but afebrile** course of several months or longer.

Chronic weight loss, dyspnea, crackles, and copious amounts of serous nasal discharge from accumulated lung fluid in an adult sheep that is afebrile are highly suggestive clinical signs of **OPA**. Clinical signs are not noticeable until a significant proportion of the lung is affected by the tumour. Occasional coughing and some panting after exercise are the earliest signs, but coughing is not a prominent sign in this disease. Emaciation, dyspnoea, lachrymation, and a profuse watery discharge from the nose follow.

Jaagsiekte has a prolonged clinical course, and is **always fatal**. Death occurs within 6 weeks to 4 months after the onset of symptoms.

Moist crackles (a series of sharp sounds) / moist rales can be heard over the affected lung areas. Even they can be heard at a distance so that a group of affected animals are said to produce a sound like slowly boiling porridge.

There is no rise of body temperature unless there is secondary infection, among which Pasteurellosis is common.

Lesions

The lesions consist of multiple foci of neoplastic alveolar type II cells in acinar and papillary patterns. The result is a pronounced thickening of the alveolar walls, and partial obliteration of the alveolar spaces by small adenocarcinomas. A certain number of mononuclear cells and lymphocytes fill the alveoli, and along with a few neutrophils, appear as an exudate in some of the bronchi.

Tumours tend to be more common in the **anteroventral portions of the lungs**. They vary from small nodules to solid coalescing masses, and are often sharply demarcated and firm. On cut surface, tumour nodules are glistening and granular, and a frothy fluid may be expressed. Microscopically, the nodules consist of cuboidal or columnar epithelial cells lining airways and alveoli and forming papillary or acinar (glandlike) structures. Because the cells have been identified originating from both type II alveolar epithelial cells and Club (Clara) cells, the neoplasm is considered a “bronchioloalveolar” carcinoma.

The peribronchiolar lymph nodules are hyperplastic and markedly enlarged. Malignancy is not common, however metastatic lesions consisting of adenomatous foci in bronchial and mediastinal lymph nodes, have been reported. The proliferative nature of the pulmonary lesion together with metastases is strong evidence that jaagsiekte is neoplastic and malignant. Secondary pneumonia, fibrinous pleuritis and/or necrotic foci are also common in the lungs of affected sheep.

Diagnosis

Both jaagsiekte and maedi/progressive pneumonia are chronic lung diseases with long incubation periods.

Maedi/progressive pneumonia is not neoplastic and is characterized by interstitial pneumonia and marked lymphocytic nodular hyperplasia.

Jaagsiekte has many points of similarity to Marsh's ovine progressive pneumonia, but one difference is the **large amount of catarrhal nasal discharge** which is characteristic of Jaagsiekte.

Wheelbarrow test: Its a diagnostic test in Jaagsiekte, where the affected sheep is held up by the hind legs and with gravity-acted animals, ample quantity of **watery mucus** (up to about 200 ml) runs from the nostrils.

Important Diseases caused by Lentiviruses

Lentiviruses affecting animals include the viruses of visna and maedi (which are very similar), caprine arthritis-encephalitis virus, feline immunodeficiency virus, bovine immunodeficiency virus and equine infectious anaemia virus (Table).

Lentiviruses produce a **chronic persistent infection** with a long incubation period, so are also known as "**slow virus infections**".

They do not require dividing cells for replication, and transcription and translation occur from non-integrated viral DNA.

Pathologically, lentiviruses establish themselves in macrophages and lymphocytes, and interfere with immune functions, so many are termed immunodeficiency viruses.

The lesions caused by different lentiviruses may vary, but most cause some combination of these: 1) lymphadenopathy with marked follicular hyperplasia, that proceed to lymphoid depletion, 2) lymphocytic infiltration, 3) interstitial pneumonia, 4) encephalomyelitis, or 5) arthritis.

Visna-Maedi

Common names: for visna-maedi are "ovine progressive pneumonia", "lymphoid interstitial pneumonia", and "chronic viral encephalomyelitis of sheep".

In 1935, a **chronic viral Encephalomyelitis of sheep** was reported from Iceland. It was named "visna" meaning shrinkage or wasting. Then, in 1939, a **chronic, progressive Pneumonia** was recognized, again in Iceland, and was named "maedi" meaning dyspnoea.

Visna maedi virus (VMV) causes a persistent infection of sheep leading to pneumonitis, demyelinating leukoencephalitis, mastitis, and arthritis, eventually killing the host. Seen mostly in **Adult Sheep** and Visna-maedi are different clinical manifestations of the same viral infection. The 'visna syndrome' is a slow, progressive demyelination (*demyelinating leukoencephalomyelitis*), whereas the 'maedi syndrome' is a slowly progressive interstitial pneumonia (*interstitial pneumonitis*). Both syndromes invariably terminate fatally.

ETIOLOGY:

Caused by **Lentiviruses** belonging to Retrovirus family, containing enzyme reverse transcriptase, an RNA-dependent DNA-polymerase

SPREAD:

Pulmonary secretions and Milk, containing infected macrophages/mononuclear cells in the **colostrum and milk** of infected ewes are the main source of natural transmission. Infection is mainly spread by the Respiratory Route.

PATHOGENESIS:

Replication of the virus occurs mainly in the **macrophages**. This leads to cell-associated viraemia, and dissemination of the virus to the brain and other organs.

Pulmonary secretions and milk containing infected macrophages are the main source of virus for natural transmission. Diseases such as jaagsiekte (pulmonary adenomatosis), which increases the number of macrophages in lung secretions, facilitate spread of visna-maedi virus.

Visna-maedi virus **avoids destruction by antibodies** through antigenic variation. The neutralizing antibodies are produced but are inefficient in selecting antigenically different viruses and therefore they are unable to neutralize the virus.

SIGNS:

Seen only in Adult Sheep, due to long interval between infection and development of clinical disease (Le., incubation period), which is usually 2-3 years. Goats do not show visna-maedi, although they are susceptible.

The clinical signs develop insidiously (gradually without being noticed) and progress slowly. The initial signs are **listlessness** (having no energy) and **loss of body condition** which progress to **emaciation and wasting**.

Signs of **respiratory involvement** are not noticeable in the early stages. **Dyspnoea** develops later. There may be coughing or nasal discharge but no evidence of excess fluid in the lungs. Clinical disease lasts for 3-10 months and the disease is always fatal.

In some sheep, clinical respiratory disease is minimal and the **major manifestation is wasting**, and the **thin ewe syndrome**.

The involvement and **induration (hardening) of mammary glands** is also gradual in onset, as the ewes are usually in their third or later lactation by the time the disease is fully manifest. In advanced cases the **udder is enlarged** and very firm.

LESIONS:

Lesions of Visna (chronic viral Encephalomyelitis)

The virus may affect both the central nervous system or the lungs in the same animal.

The lesions in the central nervous system consist of **zones of demyelination** with destruction of **paraventricular white matter** in the **cerebellum and cerebrum**. Similar lesions occur in the spinal cord. The demyelinated zones are surrounded by gliosis and lymphocytic infiltration. The meninges of both brain and spinal cord are usually infiltrated by lymphocytes and other mononuclear cells.

The lesions in the CNS result in greatly increased numbers of cells in the spinal fluid (**pleocytosis – increased cell count in CSF**) – remember differentiating from scrapie, **where no pleocytosis**.

Lesions of Maedi (Progressive Pneumonia)

In maedi, gross lesions of pulmonary form are characteristic.

The lungs do not collapse fully when the thorax is opened. **They have a dense, rubbery consistency but are not consolidated.** All lobes have a **uniform greyish colour**, and are of uniform consistency (This is in marked contrast to the differences between normal and consolidated areas in the usual type of acute pneumonia).

The lungs are **distended, appear large**, and weigh 2-5 times as much as normal adult sheep lungs (normally 300-500 g). The cut surface is dry and exudate cannot be squeezed.

The microscopic lesions show that the loss of elasticity and compressibility and the greyish colour are caused by a great increase in the **thickness of the alveolar walls**. The thickening may be so great that the alveolar spaces are obliterated. The thickening is caused by proliferation and infiltration of **reticuloendothelial** (mononuclear, macrophages etc) or **mesenchymal cells** that invade the septa everywhere. Hyperaemia of the inter-alveolar capillaries occurs in early stages. Lymph nodules occur along the course of the bronchi and bronchioles.

There is generalized **follicular hyperplasia in lymph nodes and spleen**, and lymphoid infiltrations are found in almost any organ. The **polyarthritis** is characterized by villous hyperplasia of the synovial membrane and an extensive lymphocytic and plasma cell infiltration.

One or more peculiar cytoplasmic inclusions in mononuclear cells

DIAGNOSIS:

Identification , detection or isolation of the virus

Differential Diagnosis:

- Other causes of Chronic progressive Pneumonias need to be differentiated from maedi, including jaagsiekte, in which the microscopic picture is quite different.
- Other causes of Chronic Encephalomyelitis, need to be differentiated from visna.

CAPRINE ARTHRITIS-ENCEPHALITIS (CAEV)

Is one of the most important diseases of goats caused by a lentivirus (related to the visna/maedi virus) distributed worldwide and is characterized by **ARTHRITIS** in adult goats and **Encephalomyelitis** in young goats. Although prevalence rates is up to 80% however, number of infected animals with clinical disease is usually 25%, or less.

Spread

The main route of infection is through **Colostrum or Milk**. More than 75% of kids born to infected dams may acquire infection through the colostrums and milk. The disease can be transmitted by contact both during and after the perinatal period.

Pathogenesis

Animals infected at birth remain persistently infected for life, although only some develop clinical disease. The virus infects **cells of the monocyte-macrophage** type. Shedding of the virus occurs, as infected monocytes mature to macrophages.

Disease is the result of inflammation resulting from the reaction of the host immune system to expressed virus. The lesions are **Lymphoproliferative** in nature.

The virus of CAE tries to avoid the immune system of the host through **antigenic variation**. As a result, although infected animals mount an immune response to CAB virus, the antibodies formed are unable to neutralize the virus.

Signs

The **Encephalitic Form** of the disease is usually seen in young goats 1-4 months of age. Affected kids have difficulty in abducting (taking away) the hind limbs and become ataxic (Le. unable to coordinate the muscular movements). An ascending paralysis progresses to total posterior paralysis, and ultimately tetraparesis (paralysis of all four limbs). There may be torticollis (twisted neck), and the head is held upward, or at another angle. There is only mild fever, but interstitial pneumonia can occur and be noticeable clinically.

The **Arthritic Form** is seen in adult goats. It is usually a chronic, slowly progressive disorder, developing over months. All joints are affected, but swelling of the carpal (big knee), hock, and stifle joints is most noticeable.

Lesions

Central nervous system lesions are confined to the **white matter**, and are characterized by disseminated perivascular accumulations of mononuclear cells and demyelination.

The articular lesions are characterized by a **villous proliferative synovitis** with extensive lymphocytic infiltration.

In lung, **Interstitial Pneumonia** with pronounced lymphoid hyperplasia.

Diagnosis

- Based on clinical signs, lesions and serology
- agar gel immunodiffusion test (AGID) is widely used for detection of infection.
- Other serological tests include ELISA and dot ELISA.
- Identification / Isolation of the virus into tissue culture.

EQUINE INFECTIOUS ANAEMIA (EIA)

Common name: **Swamp Fever**, Mountain fever; Equine Malarial Fever, Coggin's Disease

EQUINE INFECTIOUS ANAEMIA (EIA) is an important viral disease of horses, mules and asses (donkeys) caused by a **Lentivirus (Retrovirus)** and having worldwide distribution.

It is not only a serious economic problem, but also a useful model for the study of mechanism involved in the persistence of virus in the host, and its pathogenic effects. Once the virus enters into a susceptible animal, it can be demonstrated in the blood as long as the animal lives. Despite the immune response, the virus persists like other lentiviral infections. The disease was first recorded **in India in 1987** in an equine stud at Bangalore.

Spread

As virus is present in blood, so is transmitted mechanically by the bite of **mosquito** (*Culex* sp.) or **biting fly** (*Stomoxys calcitrans*, *Tabanus* sp.) It can even be transmitted **iatrogenically** (i.e., by a clinician) by the transfer of contaminated blood from an infected horse to a normal horse or using unsterilized fomites.

EIA is often highest in areas that are low-lying, swampy and humid hence its name.

Pathogenesis

The virus mainly affects **reticulo-endothelial system** and so localizes in blood forming & destroying organs, especially spleen, liver, kidney and lymph nodes. It disappears from tissues in periods between attacks.

Pathogenesis of EIA involves primary **entry and infection of MACROPHAGES**; destruction of macrophages and release of virus; production of antibodies to antigenic components; formation of antigen-antibody complexes, which induce fever, glomerulitis, and complement depletion, specific complexes cause haemolysis or phagocytosis by activating the reticulo-endothelial system; as virus neutralizing antibodies prevent viral multiplication in macrophages; and the virus becomes latent & horses become permanently asymptomatic. Life-long viral persistence is due to a virus-induced defect of the macrophages.

The EIA virus tries to **avoid host's immune system by undergoing rapid antigenic variation**. The EIA virus, like other lentiviruses, undergoes random mutation at a high rate, and new antigenically different variants are produced. Such variants appear rapidly and randomly. The appearance of a new non-neutralizable (neutralizing antibody not effective) variant leads to clinical relapse / recurrence.

Equine Infectious Anemia causes anemia by both Immune-Mediated Hemolysis and decreased Erythropoiesis **Hemolysis is typically extravascular** but may have an intravascular component during the acute phase. Erythrocytes of infected horses are coated with antiviral antibodies and complement 3. This binding to the cell surface results

in increased osmotic fragility (i.e., easily damaged), shortened half-life, and erythrophagocytosis. **Plasma haemoglobin** level increases and **serum haptoglobin** level decreases.

Depression of Bone Marrow and **Glomerulitis** with thickened basement membranes and increased mesangium cells is seen. This glomerulitis is the result of deposition of virus antibody complexes.

Signs

Clinical disease is commonly seen in Horses and Ponies; donkeys are symptomless. The clinical disease is usually divided into three types: acute, subacute and chronic.

ACUTE CASES (Disease at full-force) are characterized by signs of septicaemia, rapid onset of high fever (up to 108°F) after an incubation period of 1-3 weeks. The fever is accompanied by extreme weakness, excessive thirst, anorexia, depression, **oedema of the lower abdomen, and petechial hemorrhages beneath the tongue (sublingual) and anterior nares, which is pathognomonic**. Death may occur within a month.

If animal survives, disease takes up the subacute or chronic form. At the onset, Anaemia is not a prominent feature, but RBC sedimentation rate increases as there is a gradual reduction in circulating red blood cells. The normal count of **8 million / mm³ drops to about 4 million / mm³** in most cases. Anaemia is **Normocytic & Normochromic**

In the **SUBACUTE FORM** (A slower, less severe progression of the disease), the disease is manifested by relapsing (recurring) fever and recurrence of other symptoms at regular intervals and milder than acute. PCV diminishes with each relapse. Pallor (paleness) of mucous membranes indicates the loss of circulating erythrocytes, which may fall as **low as 1.5 million /mm³**.

The **CHRONIC FORM** (The horse tires easily and is unsuitable for work) may develop after the animal has passed through an acute infection. The red cell count is usually 2-3 million/mm³ below normal.

LESIONS

The nature of the lesions depends to a large extent on the clinical type of disease and the duration of illness. In other words, an animal which dies during an attack, after several aggravations characteristic of the chronic disease, shows different changes than one that dies after a single acute attack. Therefore, the lesions are described in relation to the clinical type of the disease. (Spleen-Liver-Lymph Nodes-Bone marrow-Kidney- Heart)

Acute Disease

Jaundice, oedema and haemorrhages are the main gross findings at necropsy. Oedema is most prominent in the ventral wall of the abdomen, at the base of the heart, and perirenal fat. The haemorrhages are petechial, or less often ecchymotic, and are found in the oedematous areas, or in the pleura and peritoneum.

The **SPLEEN** is nearly **twice normal size (Splenomegaly) and capsule is tense and may show petechiae**. Microscopically, the red pulp is increased in volume which results from infiltration of the cords of Billoth with mononuclear cells. These cells are believed to a rise in the reticulo-endothelium and to be immature **lymphoid cells**

The **LIVER** may be grossly enlarged, red to dark brown, with stretched capsule and may show petechial haemorrhages. **Kupffer cell hyperplasia** (swollen) contain hemosiderin stores and periportal infiltrates of lymphocytes are the most significant changes in the liver. **Siderocytes** (hemosiderin containing macrophages) in hepatic vessels.

The LYMPH NODES may be enlarged (splenic, renal, mesenteric & portal), and their changes are similar to those of the spleen. The BONE MARROW is strikingly red as the normal yellow fatty marrow is replaced by red areas of active haematopoietic marrow.

HEART-Pericardial sac may contain excessive amounts of clear or sanguineous fluid and petechiae over pericardium & epicardium. KIDNEYS are enlarged, with petechiae over the cortex. Glomerulitis with proliferation of endothelial cells; Siderocytes in glomerulus.

Animals dying during hemolytic crisis are pale with mucosal hemorrhages and dependent oedema. The spleen and liver are enlarged, dark, and turgid, and they and other organs have superficial subcapsular hemorrhages. Petechiae are evident beneath the renal capsule and throughout the cortex and medulla. The bone marrow is dark red as a result of replacement of fat by hematopoietic tissue; the extent of replacement is an indication of the duration of the anaemia.

Subacute and Chronic Disease

Oedema and Haemorrhages may occur, but are less prominent than **ANAEMIA**.

The **LIVER** is enlarged, dark brown, and firm. Affected livers show haemosiderosis. In the **MYOCARDIUM**, muscle bundles show hyaline degeneration and leukocytic (mainly lymphocytic) infiltration.

The **SPLEEN** is enlarged (Splenomegaly) and Hypertrophy of the spleen and bone marrow may be the only pathological change present. The BONE MARROW in long bones, is markedly red rather than fatty indicating haematopoiesis stimulation due to destruction of RBCs.

In **LYMPH NODES**, replacement of normal structures by reticulo-endothelial and lymphoid cells is more pronounced.

Haematological Changes

The anaemia is **normocytic and normochromic**. Anaemia occurs from a combination of haemolysis, erythrophagocytosis, and a decreased production of erythrocytes.

The **Coombs Test** checks your blood for antibodies that attack red blood cells and the results are positive.

DIAGNOSIS

A presumptive diagnosis can be made during the acute disease from the clinical signs INCL. RELAPSING / RECUURING FEVER and also from the characteristic gross and microscopic lesions at necropsy.

Equine infectious anaemia infection is diagnosed on the basis of the Coggin's Test. It is an **Agar-Gel Immunodiffusion (AGID) test**, developed by Dr Leroy Coggins in 1972 in USA, is particularly useful in detecting the presence of **antibodies (humoral response)** against virus in the serum of infected horses. (**COGGIN'S TEST**).

Confirmatory Diagnosis, BY Identification/ Detection (PCR / ELISA etc) and / or Isolation of Virus (Cell cultures)

FELINE IMMUNODEFICIENCY VIRUS Infection

Feline immunodeficiency virus (FIV) is a lentivirus. It is tropic for T lymphocytes, macrophages and astrocytes.

Spread: The virus is shed mainly in the saliva, and it is transmitted **primarily through bites**

Signs:

low-grade fever, generalized lymphadenopathy, and sometimes, diarrhoea; mostly in young cats. In chronic forms, infected cats may develop recurrent fever, lymphadenopathy, anaemia, diarrhoea, and weight loss.

Lesions:

Encephalitis, characterized by perivascular mononuclear infiltrations and glial nodules, is most likely a primary FIV lesion.

Microscopically, the **Lymphadenopathy** is characterized by early follicular hyperplasia which may later progress to marked lymphoid depletion.

Cats remain **infected for life**

BOVINE IMMUNODEFICIENCY VIRUS Infection

Caused by Bovine immunodeficiency virus (BIV), a Lentivirus, (bovine retrovirus).

Clinical findings include lethargy, mastitis, pododermatitis (dermatitis of foot), pneumonia, mycotic abomasitis, and abscessation and lymphosarcoma.