Caprine Arthritis Encephalitis: An Overview of The Global Situation and The Prevention

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Abstract: Globally, one of the diseases of economic impact and that affects the goat is Caprine Arthritis Encephalitis (CAE) caused by a virus of the Retroviridae family, genus Lentivirus, a group belongs to the Human Immunodeficiency Virus (HIV) and Ovine Progressive Pneumonia Virus (OPPV). Caprine Arthritis Encephalitis are a contagious febrile viral disease affecting the goats of all breeds, age or sex. CAE causing acute encephalitis, chronic non-suppurative arthritis of the tarsal, carpal joints, enlarged and severe hardening of the udder (indurative mastitis), with a bilateral nature that causes hypo or agalaxia, hypertrophied retromammary lymph nodes and chronic pneumonia. Caprine Arthritis Encephalitis Virus (CAEV) like all lentiviruses, has a diameter of 80-130nm enveloped particles with a dense conical nucleus, contains two copies of single-stranded genomic RNA and several viral proteins with positive polarity characterised by an extreme slowness of it is replication processes. The virus is very closely related to the Maedi-Visna Virus (MVV) which causes a very similar disease in sheep. Management and hygiene at the level of milking equipment and utensils are common act to more than one individual can reduce the transmission of contagious agalaxia in a herd. Newborns should be fed colostrum from uninfected females or with pasteurized milk. Cleaning and regular disinfection of pens are sanitary measurements planned as a prevention strategy.

Key words: Small Ruminant Lentiviruses, Caprine Arthritis Encephalitis, Maedi-Visna, Goats

Background:

Small Ruminant Lentiviruses (SRLVs) include; Maedi-Visna Virus (MVV) of sheep, and Caprine Arthritis Encephalitis Virus (CAEV) of goats [1]. These retroviruses cause chronic inflammatory disease that affects the brain, joints, lungs, and udder leading to globally significant mortality and diminish of animal production and benefits [2]. Caprine Arthritis Encephalitis (CAE) was first identified in 1980, in goat herds of the U.S. [3,4]. CAE is common in most countries where goats are raised, particularly in dairy goats, it is common in areas where production is intensive, particularly when the partitions occur in closed pens where the weather is cold [5]. In natural conditions, goats become infected in their early life, are carriers of the virus in genome throughout their lives and develop the disease with months or years later. The virus does not infect the fetous through the placenta and the greatest transmission is through colostrum and milk [6]. Although the percentage of infected animals may be high, the number of goats that manifest one or multiple clinical forms of CAE varies in each. Many factors, including the strain of the virus, the age along with the breed of the animal, the route of infection, opportunistic infections and type of management can influence

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the degree of disease. However, viral load in the infected animal seems to be the most important factor [5].

In 1974 the neurological form of CAE was described in the US. In 1978 it was reported in young goats as leukoencephalomyelitis and until 1980 the virus was isolated from animals with arthritis; in this same year, the name change from viral leukoencephalomyelitis of the goats to the present: caprine arthritis encephalitis [3]. With respect to studies on the occurrence of CAE, the prevalence in the United States was 31% in goats and 73% within herds, in Italy 81.5% of seroprevalence has been reported, while in Switzerland the prevalence among goats was 42%, in Wales was 30%, and in Turkey was 1.9%, whereas in the Sultanate of Oman was 5.1%. [7]. CAE represents a serious problem for the goat production due to it is wide distribution, high incidence in endemic areas and decline the productive life of dairy goats.

Aetiology:

Caprine Arthritis Encephalitis Virus (CAEV) is a *Lentivirus* (lente- Latin word means slow), of the family Retroviridae, that includes non-oncogenic exogenous viruses that cause various diseases of mammals [8]. The size of CAEV is approximately 80-130 nm, the symmetry of the icosahedral capside, envelope, linear diploid sense genome + 10 kb ssRNA, slow evolution, genome replicate in the nucleus and assembly in the cytoplasm. It is a virus with tropism for monocytes and macrophages, which reacts cross-way and has significant genomic homology with Maedi-Visna Virus (MVV) and Ovine Progressive Pneumonia Virus (OPPV). The virus has a lipid envelope and is inactivated by organic solvents such as ether and alcohol. It is also heat inactivated at 56 °C. The CAEV has not been shown to cause disease in man [9]. The genome of the CAEV contains three structural genes; gag, pol and env. Viral structural genes allow the production of viron proteins: gag proteins (matrix: MA, p17; capside: CA, p25; nucleocapside: NC, p14), the envelope proteins (trans-membrane: TM, gp46; surface subunit: SU, gp135) [8]. The pol gene contains information for viral enzymes reverse transcriptase (TR), integrase (IN) and protease (PR). The TR protein is responsible for copying the genome of the virus RNA into DNA. The IN protein integrates the photocopy of viral DNA into the host genome (provirus). The PR is responsible for breaking the peptide bond of the gag and pol proteins [10] (Figure 1).

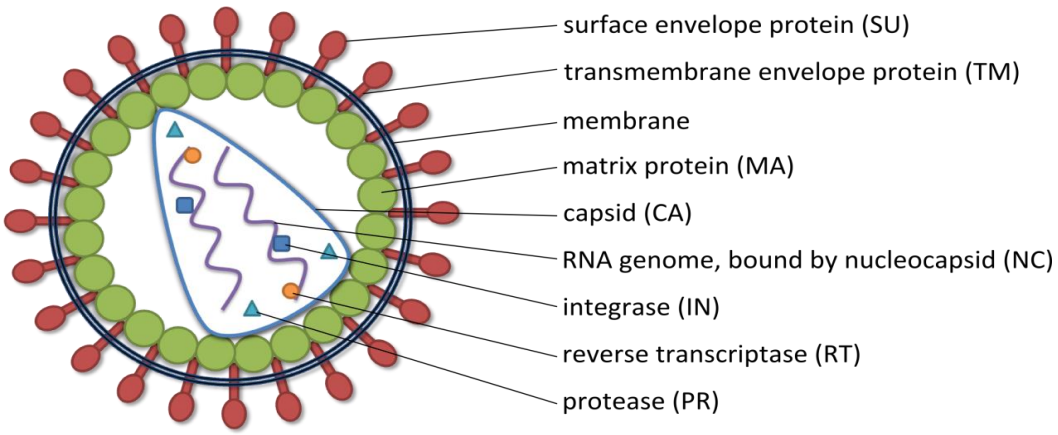

Figure 1: Illustrates the structure of *lentivirus*

The major tropism of the lentiviruses are macrophage, monocytes and dendritic cells and, nevertheless, in the tissues of other types of cells they can also be infected and act as a reservoir of the virus, these tissues include epithelial cells of the mammary gland, endothelial

cells and cells of the microglia of the central nervous system [11]. Recent studies have found two different genotypes of viruses that affect goats and lead to CAE: the *lentivirus* of genotype type B and the *lentivirus* of genotype E. Genotype B causing serious signs is transmitted both horizontally and vertically. Genotype E is known as Roccaverano strain, it is important since it is not pathogenic, there is no presentation of any signs and it can only be transmitted vertically [9].

Viral Replication:

Once the virus enters the body of the susceptible animal, it is adsorbed by the cell through interaction with cell surface receptors (1) The surface glycoproteins fuse the lipid envelope with the plasma membrane, therefore, the nucleocapsid that contains the viral RNA is released in the cytoplasm (2) Once in the cytoplasm, the RNA is copied to DNA due to the viral enzyme TR that is associated with the virion. The single stranded DNA copy transforms to a double stranded one by the same enzyme. The double-stranded DNA enters the nucleus of the infected cell (3), where it integrates with the DNA of the host cell with the help of the enzyme IN (4). To the DNA Integrated is known as provirus and serves as a template for the production of both mRNA that is translated into proteins (5), and virion RNA, which is encapsulated in the progeny virion. Therefore, the virus genome becomes part of the host genome and doubles during cell division (6), which makes it easier for viruses to be isolated from Human Immunodeficiency Virus (HIV)-positive animals many years after the original infection. The virion follows two assembly processes, one aimed at the formation of the capsid and the other at the formation of the viral envelope (7). The polyprotein formed is transported from the endoplasmic reticulum to the plasma membrane of the host cell by secretory route, where it is associated with the membrane and hydrolyzed. The translation of the gag and pol polyproteins is followed by assembly in the cytoplasm. The nucleocapsid is assembled by means of a series of proteolytic breaks of the protein produced by the viral protease, while the growth of the virions that leads to the condensation and maturation of the virus is carried out to leave the host cell (8). The virus remains inactive in monocytes and it is replication is conditioned to the maturation of monocytes to macrophages once they leave the bone marrow or the blood of infected animals to localize in the tissues. This type of replication allows the virus to remain subclinical and go unnoticed by the immune system for long periods. Goat remains seropositive for lifelong and become a continuous source of infection for susceptible individuals even though there is an immune response that constantly attacks the virus [12]. Figure (2) explain the phases of retroviral replication process.

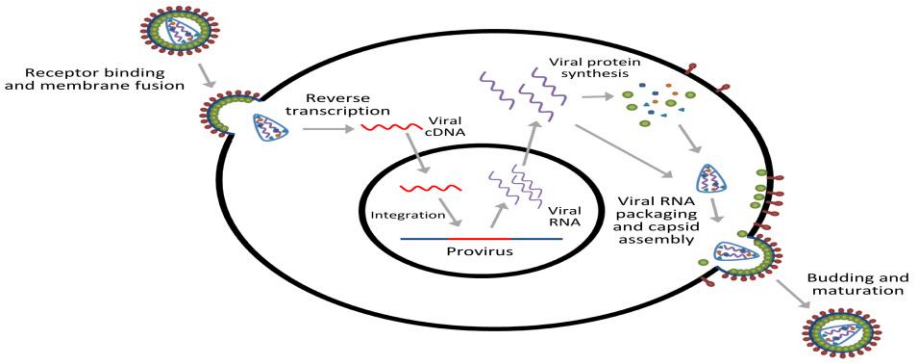

Figure 2: Phases of retroviral replication process

Pathogenesis:

Once the virus has entered the body, a brief phase of viremia develops phase of post-infection viremia [12]. SRLVs have tropism in *vivo* by monocytes, macrophages and dendritic cells. Lentiviruses of small ruminants can affect other cells in *vivo* in the nervous system, such as microglia and endothelial cells as well as fibroblasts and other epithelial cells. These cells can act as a reservoir for the virus, as is the case with the epithelial cells of the mammary gland and that contribute to the transmission between the dam and the newborn during suckling [11]. Once the SRLVs have entered the body, they infect macrophages and dendritic cells of the pulmonary or intestinal mucosa. The dendritic cells migrate to lymph nodes where the virus is transferred to macrophages, which will leave the lymph node and spread the infection [7]. It is believed that infected macrophages penetrate the bone marrow where they can affect myeloid cells, or stromal cells, which would result in the continued production of infected cells and result in chronic infection throughout the life of the animal. Replication in monocytes and macrophages does not occur until they mature in the target organs. Therefore, immature macrophages act as a "Trojan horse", as the virus clones and escapes the cellular and humoral immune response. The infection remains dormant, for a period of time that depends on the viral strain and, fundamentally, on individual susceptibility [7]. Infected cells are transported to the target organs, and once they mature, viral replication will occur. This mechanism causes that the replication of SRLVs in the tissues is constant and, therefore, the immune response that is generated in response to this replication causes a chronic inflammation that gives rise to the pathological changes observed in the target tissues of animals infected by SRLVs [7]. Accordingly, the multisystem inflammatory disease typical of SRLV infections is immunopathogenic. The main change that occurs in the affected tissues is the infiltration of mononuclear cells (lymphocytes, macrophages and plasma cells). The final phase of the pathogenesis begins when the clinical disease develops. At this point, and depending on the picture that develops, the animal can die in a short time or remain chronically [7]. Despite the high degree of infection that some herds may present, clinical manifestations are usually not overt, as there are many factors that influence the pathogenesis, mainly the viral strain, the age with the breed of the animal, the route of exposure, opportunistic infections and management conditions [7].

Transmission:

The mode of transmission is mainly through colostrum and milk, some researchers suggest that The CAE virus can also be transmitted through respiratory secretions, urogenital secretions, faeces, saliva and blood of infected animals and even semen, although there is no evidence of transmission mediated by artificial insemination. Newborn kid's can be raised free of infection if they are separated from the nanny immediately after birth and can be raised with pasteurized milk. Prolonged direct contact between infected and uninfected older goat may result in a few cross infections, increasing the incidence if female goats share mechanical milking facilities, due to milk reflux that occurs as a result of fluctuations in vacuum inside the milking system [13]. The infection has been experimentally transferred to kid's by feeding them with infected colostrum or by injection. The arthritic form of the disease has occurred experimentally in kid's extracted by caesarean section, injected with the virus isolated from the infected joints [13].

In the case of CAEV, it has been proposed that epithelial cells act as a reservoir, demonstrating that those of the epithelium of the doe oviduct are highly permissive, so they could represent an important source of infection when the ovaries are used to produce goat embryos. Likewise, the epithelial cells present in goat milk are highly permissive for the productive infection of CAEV, being able to play an important role in the vertical transmission of the virus. Also, embryonic cells are susceptible to the virus specifically, goat

embryos in the 8-16 cell stage can already be infected by CAEV provided they are not surrounded by a zona pellucida, so this layer seems to constitute a natural barrier against the virus.

Clinical Semiology:

Arthritis is a chronic hyperplastic synovitis that occurs mainly in adult goats and is noticeable in the tarsal or carpal (knee) joints, giving rise to the popular term of large knee. It can start suddenly and unilaterally or bilaterally. Goats that are affected by the CAE virus will gradually lose weight and develop poor hair and swollen joints. Goats sick with the virus remain lying most of the time, and as a result, bedsores are common. In some cases, dilation of the atlantic and supraspinosa pockets occurs. The course of the disease is long, taking several months. Arthritis can be accompanied by an increase in size and hardening of the udder and interstitial pneumonia [13].

The leukoencephalitic form of the disease mainly affects kid's 2-4 months of age. The syndrome is characterised by posterior uni or bilateral paresis and ataxia. In the early stages, the evolution of the virus is short and agitated, followed by weakness and eventually a tendency to decubitus. In animals that are still able to stand, there may be a marked loss of proprioception on one of the hind legs. When there is already an affectation at the cerebral level, the animal shows an inclination of the head, torticollis (wry neck) and march circle. Kid's with unilateral posterior paresis usually progress to bilateral posterior paresis in about 5 to 10 days. The paresis generally extends to affect the anterior legs, such that tetraparesis occurs. Most kid's are sacrificed. The interstitial pneumonia that commonly accompanies the virus in its nervous form is usually not so severe as to be clinically evident [13]. hard udder or indurative mastitis, which is not necessarily caused by the CAEV, develops a few days after delivery. The udder is firm and hard, but you cannot get milk. Recovery is never complete, but there may be some gradual improvement [13].

Clinical Pathology:

The synovial fluid of the affected joints is generally brown and stained red, and the number of cells increases to 20,000/ µl with 90% of mononuclear cells. Cerebrospinal fluid may show an increase in protein concentration. Radiographically, there are soft tissue swelling in the early stages and calcification of the periarticular tissues and osteophyte production in later stages [13].

Post-Mortem Findings:

In the arthritic form there is emaciation and chronic polysinovitis. There is evidence of degenerative joint disease in almost all joints. Local lymph nodes are microscopically enlarged and diffuse interstitial pneumonia is usually present. In the pleural form, the diagnostic lesions are in the nervous system and affect the white matter, especially the cervical spinal cord, and sometimes the cerebellum and brainstem. The lesion is a non-suppurative demyelinating encephalomyelitis. There is usually a mild, diffuse interstitial pneumonia [13]. It was possible to observe the presence of macrophages in the male reproductive tract, in particular in the acinar light of the adjoining glands, ampulla, seminal vesicle and bulbo-urethral, these defense cells can be found in both healthy and diseased animals. This observation suggests that the epithelia of the reproductive tract of infected buck, especially those of the attached glands, can serve as multipliers of the CAE virus and promote its dissemination by semen [14].

Nucleic Acid Recognition Methods:

Nucleic acid recognition methods for the detection, quantification and identification of CAE provirus DNA using the standard polymerase chain reaction (PCR) followed by Southern blotting, in situ hybridization or cloning and sequencing of PCR products. Viral genome can be extracted from different tissues such as lung, synovial membranes, and udders. Standard PCR techniques for the detection of CAE provirus DNA in cells and tissues routinely used in many laboratories and are generally used as ancillary tests to determine the status of infection in animals that can not be definitively diagnosed by serology. Real-time PCR techniques are beginning to be used in a few laboratories and these tests, in addition to determining the status of the infection, also quantify the amount of CAE provirus in an animal. In addition, the molecular techniques of PCR, cloning and sequencing also allow to know the specific strains of a country or region, which can influence what type of serological test and antigen should be used.

An important question about the use of PCR is it is specificity. Sequencing is the best test of specificity in the validation of PCR-based tests and is recommended by the World Organization for Animal Health [5].

Differential Diagnosis:

Due to the clinical, morphological and productive behavior characteristics, the CAE must be differentiated from other types of locomotor disorders such as lameness due to arthritis and traumatic synovitis, fractures, ligament tearing, meniscal rupture, osteoarthritis and arthritis of infectious origin produced by coliforms, *Staphylococcus*, *Streptococcus*, *Mycoplasma*, *Chlamydia* and *Choriobacteria* spp. [13]. From the respiratory point of view, CAE should be distinguished from caseous lymphadenitis, mycoplasmosis, contagious pleuropneumonia and pasteurellosis pneumonia. For the nervous form, they must be distinguished from toxoplasmosis, nematodiasis, trauma, copper deficiency and congenital anomalies of the brain and spinal cord, in addition to those specific diseases of the central nervous system such as listeriosis and polioencephalomalacia [13].

Treatment:

The treatment against caprine arthritis encephalitis has not been successful, goats can be treated with broad-spectrum antibiotics to avoid complications against opportunistic bacteria, the arthritic form can be improved by putting a thick layer of bed and administering anti-inflammatory drugs such as corticosteroids [13].

Prevention and Control:

CAE infection is tricky to control owing to the capability of the aetiology to integrate into the genome of the host, provoke constant contagions and evade neutralization. The vaccination tries have sometimes triggering increased viremia with more acute illness. Up till now, the control depends on the identification of infected animals and keeping them physically separated from uninfected animals. Newborn kid's can be raised free of infection if they are separated from their dam immediately after birth, feeding them with pasteurized milk and analyzing them serologically at regular intervals to ensure they remain free of the infection. The common practice of feeding kid's with colostrum from several goats should not be allowed, since the colostrum of infected females contains antibodies, but the infectivity of the virus, which is also present, is not limited. Continuous contact between adults who are infected with the virus will facilitate horizontal transmission and may reduce the effectiveness

of an eradication program based on the control of vertical transmission in young's [13]. Detecting positive reactors in seminal plasma is a necessary control measure that could reduce the spread of the disease [14]. The intake of colostrum in the first days of the kid's life is essential for it is survival. These animals are born devoid of immunoglobulins (Ig), since in this species the placenta prevents the transfer of Ig from the mother to the fetus, so that the colostrum provides them with the necessary ones to survive until their endogenous production begins.

In the practice of artificial lactation, the kid's must be separated from their dams after the birth with the objective of minimizing the maternal-filial relationship established in the first hours after birth. Also, management is especially important in areas where colostral transmitted diseases such as CAEV are present. Colostrum pasteurization plays a fundamental role in the prevention of this type of diseases. There are findings that demonstrated the inactivation of the CAEV after pasteurization at 56 °C for one hour. Refrigeration is a good method of preserving goat colostrum for at least three months. The methods of colostrum defrosting have a lower effect on the concentration of IgG of the same as the successive freeze-thaws. Pasteurization has a negative effect on the concentration of colostrum IgG, as well as the exclusive use of commercial colostrum implies a high risk to failure of passive transfer (FPT) of immunity. Moreover, apply the method of colostrum feeding (twice daily intakes for two days, each taking 5% of birth weight) does not show differences between chilled colostrum and frozen in the first month of life.

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