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Lumpy Skin Disease: A Review on Etiopathogenesis, Transmission, Diagnosis and Treatment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The lumpy skin disease virus (LSDV), which can cause serious infections and inflict significant economic losses, is the cause of lumpy skin disease (LSD), a viral condition affecting cattle. LSD is a fast-spreading disease that has lately expanded from Africa to Asia and spread to Europe, raising growing concerns on a worldwide scale. In India, recently LSD is on the rise affecting cattle and reducing the production of milk. The virus belongs to the Capripoxvirus genus of the Poxviridae family, it is transmitted by both vector and non-vector-born models. In cases of severely affected cattle, nodular lesions are displayed all over their bodies, but in cases of less severe disease, the

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lesions were limited to the back, thurl, udder, hip, and pin bone. To reduce the spread of LSDV, various evaluations of diagnostic technologies, treatment options, and the efficacy of vaccinations have been investigated. Among various diagnostic assays, ELISA, IPMA, and PCR have shown more promising results, prevention and vector control is the ideal strategy for controlling this disease.

Keywords: LSDV; capriproxvirus; vector born model; diagnostic assays; vaccination.

1. INTRODUCTION

Lumpy skin disease (LSD) is a highly contagious skin disease in cattle brought on by the Lumpy skin disease virus (LSDV). Most outbreaks have been seen in the springtime, when insect activity happens at its highest. Blood-feeding arthropods including Rhipicephalus, Stomoxys, Amblyomma, and Aedes are the prime source of LSD [1]. This disease is distinguished by many skin nodules, lesions on the mucosa of the airway and gastrointestinal tracts, pyrexia, loss of weight, and malaise. It is associated with low to moderate mortality however, trade in animals and loss of productivity, milk production, is significantly impacted by LSD, particularly in areas where the disease is regional and immunization is certainly not a common practice which leads to severe economic losses to the farmers and also due to treatment, surveillance, and restrictions on trade, the disease can have a consequential financial impact in LSD-free countries [2].

The first instance of this disease was reported in Zambia (1929) in Africa [3]. In Africa, LSD has spread like wildfire, but for over 80 years, it has been largely limited to Africa, occasionally causing epidemics in the Middle East [4]. The disease's first known outbreak, in Israel, was in 1989, making it the first nation outside of Africa. However, the disease spreads beyond Africa to Europe and the Gulf Region, where it severely damages livestock businesses. Numerous LSD cases have recently been recorded in Myanmar, China, Bhutan, Vietnam, Hong Kong, India, and Nepal [5]. The disease was first reported in India in 2019 in eastern regions, notably West Bengal and Odisha, and slowly spreading to neighboring states. The most severely afflicted state in India is Punjab, where over 3,000 cattle have died, followed by Rajasthan with over 2,000 and Gujarat with over 1,000 cattle dead [6] leading to high economic loss to the farmers and government. Unknown factors may have contributed to the disease's spread to India, including border movement of cattle or vectors from nearby nations.

The disease is mainly transmitted by blood-sucking arthropods which include both insects and non-insects, the spread of the virus is influenced by the strength and direction of wind over longer distances [7]. The disease is majorly identified by observing clinical signs (mortality and morbidity), in which most cases the disease lately recognizes by the farmer which leads to cattle death and economic loss. The disease's recurrent outbreaks and reappearance in different areas of the world emphasized the significance of reviewing the biology of the disease, the viral transmission mechanism, and improved prophylactic and effective control approaches. The current review provides a comprehensive description of the disease etiopathogenesis, diagnosis, and treatment in cattle.

2. ETIOPATHOGENESIS

The lumpy skin disease virus (LSDV) is the cause for lumpy skin disease (LSD) belongs to the genus Capripoxvirus (CaPV) under the family Poxviridae [8], the majority of domestic animals, except for dogs, are affected by viruses belonging to this family (Qunin et al., 2016) Entomopoxvirinae, which infects invertebrate hosts, and Chordopoxvirinae, which infects vertebrate hosts, are the two subfamilies that make up these family (Qunin et al., 2016) belongs to dsDNA group (Fig. 1). The lumpy skin disease virus (LSDV), goatpox virus (GTPV), and sheeppox virus (SPPV), which infect cattle, goats, and sheep respectively, belong to the three phylogenetically distinct virus species found in the genus CaPV, which comes under the Chordopoxvirinae subfamily [9].

LSDV is an enveloped virus that has a brick-like form and is 320 x 260 nm in size. The LSDV contains double - stranded DNA in which the genetic material is 151 kbp in size and is made up of a central coding area with complicated symmetry, surrounded by undistinguished and altered 2.4 kb that form the viral genome's last ends and 156 presumptive genes [10], and double stranded DNA is covered by a protein

layer (Fig. 2). The last regions of the genome are a site for the genes that regulate host range, pathogenicity, and immune evasions. The virus contains thirty structural and non-structural genes that are 97% nucleotide, identical to homologs of the sheeppox and goatpox viruses. The LSDV varies from other Capripoxvirus species in that it possesses the unique gene LSDV132 in addition to 146 conserved that are encoded with data on mRNA synthesis, DNA replication and transcription [11], nucleotide metabolism, virulence, and host range [10,12,13].

The virus typically resists both physiological and inorganic agents (active compounds) and holds on steadily between 6.6 and 8.6 pH, but it is more susceptible to environments with higher pH [14]. Although the virus seems to have some heat resistance, it can become inactive after being exposed to heating conditions of 55° Celsius for two hours or 65° Celsius for thirty minutes [15]. The virus's viability is preserved at low temperatures (-80oC) and can be reactivated after being frozen for ten years [16]. LSDV exhibits susceptibility to detergents including lipid solvents, 1% formalin, 2% phenol, 2-3% sodium hypochlorite, ether, 0.5% quaternary ammonium compounds, and diluted iodine compounds [16,17].

In natural conditions, the disease incubates for two to five weeks, whereas in experimental conditions, it takes seven to fourteen days. Acute, sub - chronic, and chronic are the three conditions that LSD might be seen in infected cattle. Biphasic fever is the first sign of the disease in which a. fever of more than 40.50 degrees Celsius may last for up to a week [18]. Clinical signs of an acute condition include emaciation, lachrymation, a sharp decrease in milk output, and swollen, easily palpable sub-scapular and prefemoral lymph nodes that appear within two to three days of the onset of fever. Later on, four to seven days after entry of the virus confined lump of one to three cm plaques, also excruciating nodular lesions, engorgement could also be seen on the animal body, notably on the outer dermal layer of the snout, nares, withers, legs, tail, scrotum, dewlap, eyelids, nasal and oral mucosal track [19].

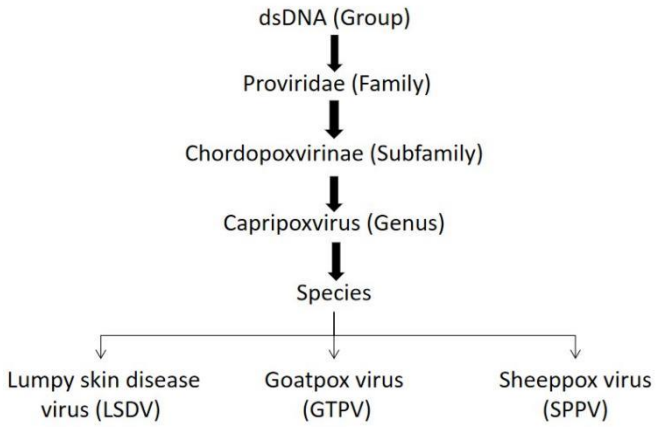

Fig. 1. Classification of lumpy skin disease virus

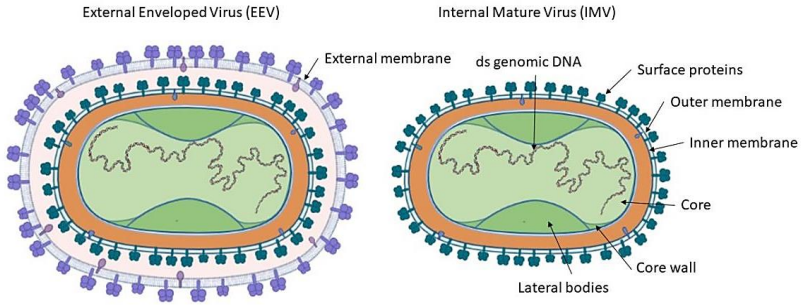

Fig. 2. Illustration on morphological structure of lumpy skin disease virus

Fig. 3. Severely affected cattle with multiple skin lesions[22]

In a critical case, the skin on the body develops more than 100 nodules, and this stage lasts for seven to twelve days. Deep nodules affect the whole skin structure, including the dermis, epidermis, nearby subcutaneous tissue, and muscle tissues [12], with the appearance of very distinctive, 10–50 mm-diameter nodular skin lesions, the number of lesions might vary from a few in mild infection to numerous in animals with severe infection (Fig. 3). The lesions then develop into papules, vesicles, and eventually scab development. The cornea on both eyes can occasionally develop severe pain ulcerative lesions, which in the worst instances might result in blindness. Sloughing of the lesions may result in holes from the "sit fast" lesion, which can then invite bacterial invasion and invasion by screwworm flies, both of which can result in secondary bacterial infections and lameness [12,20]. In the six to eighteen days after infection, lethal nodes are seen in the mucus membranes of the nasal and oral cavities causing mucopurulent nasal expulsion and uncontrolled salivation, both secretions contain high concentrations of the virus [18]. Nodules on the skin would last for several months. Abortion occurs during the infection's acute phase [12]. Forty- two days post infection following a fever, viral presence is seen in the semen [21]. Pox lesions can be seen on the surface of nearly every internal organ and across the whole digestive and respiratory systems in a postmortem examination of infected cattle [22].

3. TRANSMISSION

The mechanism of LSDV transmission is help to assess the virus epidemiology, which aids in developing a strategy for gradual disease control and eradication.

3.1 Non-vector Transmission

The first instance of LSD is frequently linked to the transport of cattle, whether legally or illegally, across ranches, regions, or even nations. In reality, cattle movements may enable the virus to cross large distances. At normal the temperatures, virus may continue to exist for a very long time, especially in dried scabs. According to reports, the virus can apparently survive in dried crusts for up to 35 days, and in nodules of necrotic skin for up to 33 days. Despite the lack of experimental evidence, it is likely that without adequate cleaning and disinfection, the farm or natural settings stay contaminated for a considerable amount of time. Infected animals with lesions on the skin, mucosal membranes of their mouth and snout expel the virus in their saliva and rhinorrhea, which can infect other animals while sharing feed and watering basin indirectly [23]. Since the virus can persist in the semen of infected bulls for up to 42 days after infection (Fig. 4), natural breeding or intracytoplasmic sperm injection may put females at risk for infection [24]. The virus is thought to spread from an infected mother to her calf by milk feeding and skin abrasion [18]. In literature, intrauterine lumpy skin disease virus transmission has been described [7]. When a single needle is used for mass vaccinations and the virus is picked up via skin scabs or crusts, this is known as the iatrogenic pathway and is another way that viruses can propagate [16].

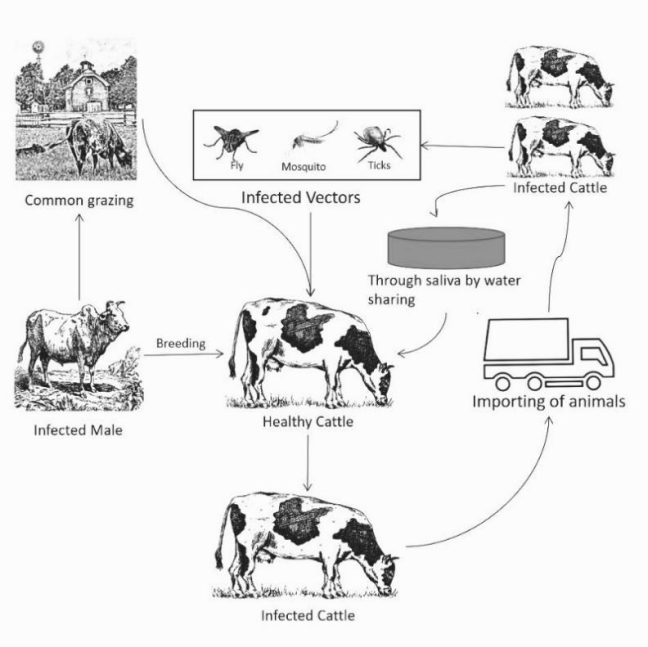

Fig. 4. An illustration of potential LSDV transmission methods [22]

3.2 Vector Transmission

The primary vector will most likely differ between geographical regions and ecosystems. The fact that most LSD outbreaks take place in the spring when arthropod activity is at its peak, could indicate that various types of vectors, particularly those that feed on blood, are involved in the spread of the virus [25, 26]. The numerous local blood-feeding arthropods which switch hosts during feeding spread disease to a large distance which are corresponding to what distance insects can fly (typically about fifty km). The ability to transmit LSDV has been demonstrated by the common stable fly (Stomoxycalictrans and Biomyiafasciata), mosquito (Culexmirificens and Aedesnatrionus), and various African tick species (Rhipicephalusdecoloratus,Rhipicephalusappend iculatus, and Amblyomma spp.). It was found that the virus and viral antigen that causes disease are found in several insect organs, such as haemoglobin, salivary glands, and other internal organs [27-29].

4. DIAGNOSIS

LSDV infection can extend from acute, subclinical (asymptomatic) to clinical (severe) conditions [4]. Even when infected during experiments, a sizable portion of the animals may develop a subclinical infection [4,30]. Based on the disease's highly distinctive clinical symptoms, a speculative diagnosis of the condition of the disease can be identified. For the detection and confirmation of the disease, numerous applications of diagnostic laboratory techniques, differential diagnoses, and clinical indicators have been developed [31]. The effectiveness of disease control, elimination, and prophylaxis often depends on the availability and quality of diagnostic tests [32]. The isolation and identification of the virus are essential for the detection of LSD in a new area. Preliminary to the generation of neutralizing antibodies, samples for viral isolation should be obtained within seven days of the development of clinical symptoms. The permissible cell culture range for LSDV is rather limited, it has typically been cultured on ruminant-derived primary cells, including fetal bovine muscle cells, lamb testis cells, and fetal bovine skin cells [33]. The proliferation of LSDV has been demonstrated to be supported by the continuous ovine testis cell line OA3.Ts [34] nevertheless this cell line has a low passage count, slow growth, and an undetermined pestivirus status. Additionally, more instances of the virus proliferation on Madin-Darby bovine kidney (MDBK) cells are being reported [33,35,36]. This cell line was preferred because it was obtained from cattle, had a high rate of growth, and suitable for Cas9 editing [33].

4.1 PCR

The generic real-time PCR method detects the virus more precisely than other diagnostic methods. Real-time PCR is specific, easy to use,

and sensitive, making it possible to test for CaPV quickly and in high quantities. Real-time PCR provides a higher efficiency than conventional gel-based PCR testing for the detection of CaPV [37]. According to experimented studies, samples taken from skin lesions give better results in PCR than those taken from blood due to the larger quantity of virus present in the lesions. Species-specific PCR methods can differentiate the three species belonging to genus CaPV [38], this is also a valuable tool if characteristic clinical LSD signs are seen in native grazing animals in a nation where all species Capri pox members are endemic [18,39,40].

4.2 Electron Microscopy

Even though it is not frequently done, an electron microscopy examination can be useful for primary diagnosis. Examining the virus using electron microscopy on biopsy samples taken from affected skin or mucous membranes that have been negatively stained. The results of electron microscopy are typically achieved in a single day, despite the fact that it requires expensive equipment and specialized laboratory technicians. It also lacks sensitivity and is primarily regarded as a confirmative tool.

4.3 ELISA

It is a notably practical technology used in seroepidemiologic studies of capripoxvirus infections. It is important to note that the time between vaccination and serum collection may alter the analytical specificity and sensitivity of the test [41]. ELISA strategy has been developed based on employing peptides, entire (inactivated) viruses [42], or purified / recombinant proteins such as P32 [43-45]. However, the difficulties connected with the purifying procedure, along with the low expression level of P32 due to poor solubility, would provide a significant challenge. Later, the inactivated, sucrose density gradient semi - purified SPPV was employed as a coating antigen in the established indirect ELISA and produced positive results when screening serum from all three host species [42]. In contrast to IFTA or VNT, the ELISA has indeed been proven experimentally and demonstrated superior sensitivity and precision [46].

4.4 Immuno- peroxidase Monolayer Assay (IPMA)

An IPMA-based test has been identified for possible application in the diagnosis of LSD. It is a low-cost and simple test with great sensitivity and conforms to low biosafety levels [47]. The novel LSDV-IPMA had a peak digital signal processor (DSP) and could identify antibodies preliminarily in contrast to the ELISA [32]. The benefits of the test include its ease of use, minimal resource requirements, and absence of a necessity for large quantities of (purified) antigen without sacrificing sensitivity [48] and selectivity. Recently, an immunoperoxidase monolayer assay (IPMA) utilizing a peroxidase staining approach was created for the assessment of total binding and neutralized antibodies against LSDV on OA3.T cell cultures [32,33]. According to a study, it has been demonstrated that the LSDV-IPMA plates can be safely stored at the right temperature for up to two months. The recently developed IPMA is adaptable (can be used for SPPV, GTPV and LSDV), incredibly sensitive, and precise, it is also well suited for routine screening of small to medium sample sets, particularly early after infection or immunization [32].

4.5 Differential Diagnosis

Other disease produce symptoms similar to lumpy skin disease. It is critical to establish a proper diagnosis to adopt the most efficacious preventative and control strategies for susceptible herds. LSD is recognized in animals by the emergence of lumpy nodes on the surface of the body, mouth, eye, oral, and nasal membrane, almost the same clinical symptoms have been observed in other diseases, raising LSD suspicions. Although it has a shorter clinical course than LSD, pseudo-lumpy skin disease, which is brought on by the bovine alpha herpes virus, develops swellings on the skin that resemble lumpy nodes which are often confused with LSD signs. Besnoitiosis, Bovine virus diarrhoea/mucosal disease, Bovine malignant catarrhal fever (Snotsiekte), Demodicosis (Demodex), Rinderpest, Oncocercariasis, Insect bite allergies are all deliberated as the differential diagnoses for LSD [49].

5. TREATMENT

There is currently no cure for LSD that works effectively. Antibiotics are nevertheless provided to infected animals in order to stop further bacterial invasion and other supportive drugs in order to treat the clinical symptoms. Vaccination is the only reliable method of disease prevention [22]. Depending on the disease's severity, antibiotics like fluoroquinolones, tetracyclines, penicillins, and cephalosporins are advised for 5

to 7 days to prevent further microbial infections on the skin abrasions [22,50]. Non-steroidal anti-inflammatory drugs (NSAIDs) and Antihistaminic medication administration are also recommended. It is also suggested to topically apply an antiseptic to the skin to prevent insects and bacterial infection. An antipyretic drug, such as paracetamol, is administered to lower fever. The disease is considered to be difficult to eradicate, and further delays in culling afflicted animals raise the risk of propagation of disease [41]. By educating veterinarians and livestock workers, disease transmission could be slowed down since they would be better equipped to diagnose clinical cases quickly [51].

5.1 Vaccination

The most efficient way to stop LSD from spreading is to vaccinate cattle with a proven vaccine, along with mobility limitations and the removal of afflicted animals, especially if preemptive before the virus enters an area or country at risk [52]. The best medical prevention for LSD is prophylactic vaccination with homologous (Neethling strain) or heterologous live attenuated vaccine (Sheep/Goat pox vaccine) [53-55]. Companies prepared vaccinations based on various LSD virus strains. It is either based on the SIS Neethling type (Lumpyvax, MSD Animal Health-Intervet, South Africa) or the Neethling strain like the LSD Vaccine for Cattle (Onderstepoort Biological Products; OBP, South Africa) [11] and Bovivax (MCI Sante Animale, Morocco), although some vaccinated animals have developed nodular skin after being subjected to the virus, there were more clinical cases in the unprotected herd than in the vaccinated herd [56,57]. Furthermore, inactivated vaccines could be used in the final stage of disease eradication as part of a strategy that begins with live vaccines [58]. The potential of coinfection should be taken into consideration when using live vaccinations because there is a possibility of recombination between the wild field strain and the vaccine [26].

5.2 Prevention and Vector Control

Control of cattle movement and confinement of the cattle are the first urgent actions to be put in place when a disease is first found in a nation or area. This also applies to high-risk areas close to neighboring nations that have an LSD problem. Transportation should be kept to a minimum in these locations, and in high-risk areas, clinical surveillance should be implemented. The migration of vectors brought on by the dominant winds may spread disease. Since vector control cannot stop the escalation of LSD or the infection of humans, it should be seen as a supportive strategy rather than a preventative one. In addition to other pest control techniques, routine application of sprinkling insect repellents, and pesticides for livestock can help control vectors in farm buildings and grounds.

5.3 Awareness

Cooperation between farmers and other participants in the cattle value chain is essential for effective disease control. Along with medical prophylaxis, a number of additional zoo hygienic prophylactic measures are effective in preventing LSD in domestic animals. These include limiting movement, grazing restrictions [22,55], euthanizing severely afflicted animals [1], properly disposing of infected carcasses [41,51], cleaning contaminated areas with disinfectant [32], using pest repellents [22], enforcing strict quarantines, and finally, disease awareness campaigns directed at veterinary professionals and students as well as farmers, herdsmen, livestock dealers, transporters, and artificial inseminators.

6. CONCLUSION

Predominantly affecting cattle and buffalo; LSD is a significant transboundary disease that causes substantial economic damage for both the country and farmers. It is a vector-borne disease mostly spread by arthropods that feed on blood. Up until 1990, the disease was only seen in African nations, it eventually expanded to other nearby nations. More recently, an epidemic of the disease occurred in India, which caused significant economic damage, the causes of the outbreak are currently being looked into. The disease is distinguishable by lumps on the body of the cattle, such as the hip and pin bones, back, udder, eye, and nasal mucous tract. There is no specific treatment is developed, only drugs are given to alleviate the symptoms of the disease. To lessen the spread of the disease, vaccination and vector control are the only preventative measures that are used because no particular treatment has been established.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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