Pathogenesis of Lyssa Virus

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ABSTRACT

Lyssa viruses, belonging to the family Rhabdoviridae, are notorious for causing rabies, a fatal zoonotic disease affecting various mammalian species, including humans. This review delves into the taxonomy, evolutionary relationships, and phylogenetic analysis of lyssa viruses, emphasizing the importance of accurate classification for effective disease management. The lyssa virus genus, within the Rhabdoviridae family, consists of species and genotypes designated by the International Committee on Taxonomy of Viruses (ICTV). Notable strains include Rabies lyssa virus (RABV), Lagos Bat lyssa virus (LBV), Mokola Virus (MOKV), Duvenhage Virus (DUVV), and European Bat Lyssa viruses (EBLV). Geographic distribution patterns reveal variations in prevalence across continents, with Africa hosting a multitude of lyssa virus species. Factors influencing distribution include bat species diversity, human-animal interactions, and vaccination coverage. Prevalence challenges arise from inadequate vaccination, limited post-exposure prophylaxis access, and socio-economic factors. The lyssa virus transmission routes encompass bites, licking, and even airborne infections, posing risks to both animals and humans. The pathogenesis unfolds through primary replication in local tissues, dissemination to the central nervous system, and neuroinvasion. Distinct clinical manifestations, including furious and paralytic rabies, result from the virus's spread within the central nervous system, causing varied neurological symptoms. The immune response involves both innate and adaptive components, with the lyssa virus employing immune evasion strategies, such as inhibiting the NF-kB pathway and interfering with type I interferon signaling. Diagnostic methods include serological assays, RT-qPCR, and histopathological examination. Prevention strategies focus on animal management and vaccination. Post-exposure prophylaxis, wound cleaning, and active vaccination with vaccines like Human Diploid Cell Rabies Vaccine (HDCV) are essential for treating potential lyssa virus exposure.

Keywords: Lyssa viruses, Rabies, Taxonomy, Geographic distribution, Immune response

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1. INTRODUCTION

Lyssa virus is basically a genus of the Rhabdoviridae family. Having single-stranded negative sense RNA, this virus infects mammals and provokes viral encephalomyelitis, which is commonly known as Rabies (Rudd and Davis 2016). The shape of the lyssa virus is like a bullet shape, and its size varies from 100 to 300nm (Lawaski et al. 2004). Mostly, the lyssa virus has five viral proteins: nucleoproteins are the first one, then polymerase, glycoprotein, matrix protein and phosphor protein. This virus has five serotypes:serotype 1, rabies; Lagos bat virus indicates serotype 2; Macula represents serotype 3, serotype four had been seen in Duvenhage and last serotype 5 found in the European bat Lassa virus (Bourhy et al. 1998). Being obligatory parasites, lyssa virus accomplished their life by controlling the biosynthetic machinery of the host cell (Rupprecht et al. 2011). The virion of lyssa virus consists of a central rib nucleoprotein complex (RNP), tightly coiled and with helical symmetry. RNP consists of a ribonucleic acid (RNA) genome. It is consisting of approximately 12,000 nucleotides, single-stranded, negative polarity that is closely associated with multiple copies of nucleoprotein (N protein) and polymerase (L protein) and its cofactor, phosphoprotein (P protein). A bullet-shaped lipoprotein envelope, derived from the host cell, surrounds the RNP during budding, and inside this envelope are many button tips, each of which is a glycoprotein (G protein) trimmer. The fifth viral protein, matrix protein (M protein), lies between the envelope and RNP. This can be built into the inner layer envelope, in the central axis of the RNP, or both as mentioned in the Fig. 1 (McColl et al. 2000).

Lyssa viruses, members of the family Rhabdoviridae, encompass a group of viruses known for their ability to cause rabies, a fatal zoonotic disease affecting numerous mammalian species, including humans, which remains a significant global public health concern. Accurate taxonomy and classification of lyssa viruses play a pivotal role in effective disease management and control. According to (Smith et al. 2019), understanding the taxonomic relationships within the Lyssa virus genus is crucial for studying the genetic diversity and evolutionary history of these viruses.

2. LYSSA VIRUS TAXONOMY

2.1. FAMILY RHABDOVIRIDAE

The lyssa viruses belong to the family Rhabdoviridae, which encompasses a diverse group of enveloped, single-stranded RNA viruses (Bourhyet al. 2005). The classification of lyssa viruses within this family is based on their structural and genetic characteristics, as highlighted by (Johnson et al. 2011).

2.3. GENUS LYSSA VIRUS

Within the family Rhabdoviridae, the genus Lyssa virus is comprised of viruses that primarily infect mammals, causing rabies. The classification of lyssa viruses into the genus was proposed by based on their shared antigenic properties and pathogenicity (Dietzscholdet al. 2003).

2.4. SPECIES AND GENOTYPES:

Lyssa viruses are categorized into different species and genotypes based on genetic and antigenic characteristics. The International Committee on Taxonomy of Viruses (*ICTV*) has designated several

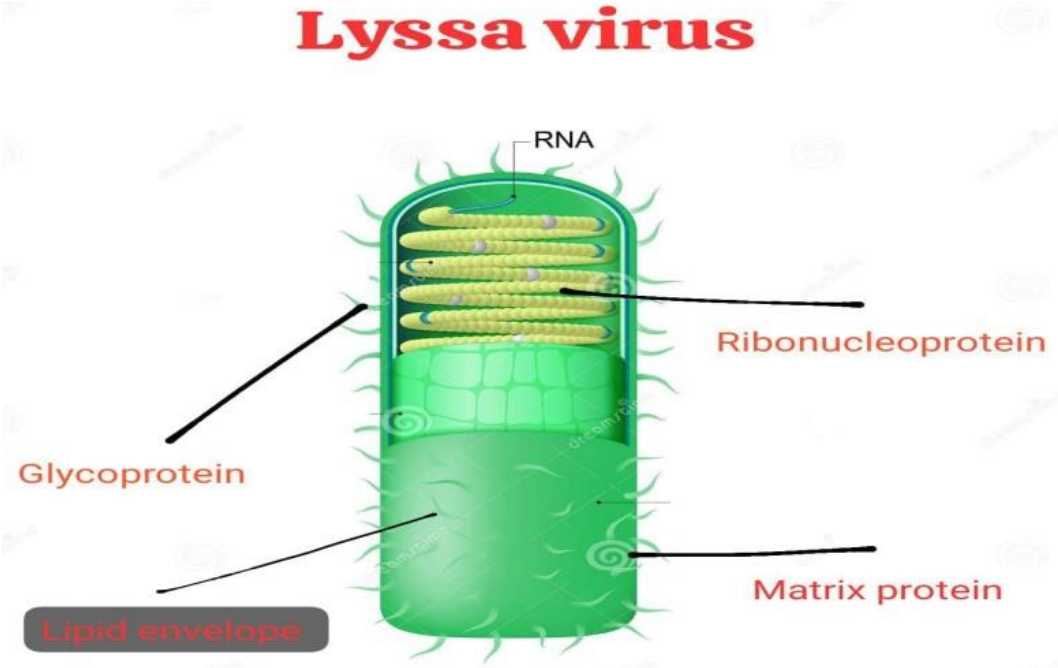

Fig. 1: Morphology of Lyssa virus

lyssa virus species and genotypes.Examples include the Rabies lyssa virus (RABV) species, which encompasses multiple genotypes such as the classical RABV, (Banyard 2017), and the Lagos bat lyssa virus (LBV) species (Markotteret al.2006).

2.5. EVOLUTIONARY RELATIONSHIPS AND PHYLOGENETIC ANALYSIS

2.5.1. MOLECULAR TECHNIQUES IN LYSSA VIRUS CLASSIFICATION

Advancements in molecular techniques have significantly contributed to the understandingof lyssa virus taxonomy. Molecular analyses, including whole-genome sequencing and phylogenetic reconstruction, have provided insights into the evolutionary relationships among lyssa viruses (Badraneet al. 2011).

2.6. PHYLOGENETIC STUDIES AND CLADE ANALYSIS:

Phylogenetic studies based on viral genomic sequences have helped elucidate the evolutionary relationships among lyssa viruses conducted a comprehensive phylogenetic analysis of lyssa viruses, identifying distinct clades and their relationships with different host species (Banyard et al. 2013).

3. TYPES AND STRAINS

Understanding the different types and strains of lyssa viruses is crucial for effectiveprevention, control, and management of associated diseases.

3.1. RABIES LYSSA VIRUS (RABV)

Rabies lyssa virus (RABV), the type species within the genus Lyssa virus, has a globaldistribution and various identified strains, including classical rabies virus (RABV). RABV is responsible for the majority of

human rabies cases worldwide, with transmission primarily occurring through the bite of infected animals, especially dogs and wildlife (Hemachudhaet al. 2002).

3.2. OTHER LYSSA VIRUS TYPES AND STRAINS

3.2.1. LAGOS BAT VIRUS (LBV)

Lagos Bat Virus (LBV) is associated with bats in Africa and has potential zoonotic implications. LBV was separated from multiple species of bat, including bats along with fruit straw-like color (*Eidolon helvum*) and the water mongoose (*Atilaxpaludinosus*), and has been linked to spread of rabies in humans, highlighting its importance in the region's public health (Markotteret al. 2006).

3.3. MOKOLA VIRUS (MOKV)

Mokola Virus (MOKV) is another lyssa virus found in Africa, primarily associated with bats. MOKV has been detected in both insectivorous and frugivorous bats, including the African straw-colored fruit bat and the banana pipistrelle bat. Although it has a more limited geographic distribution compared to RABV, it poses a significant risk to human and animal health in affected regions (Marston et al. 2012).

3.4. DUVENHAGE VIRUS (DUVV)

Duvenhage Virus (DUVV) is prevalent in insectivorous bats in Africa and is associated with human cases of rabies. DUVV was separated from multiple species of bat, containing the Egyptian slit-faced bat (Nycteristhebaica) and the Rufous mouse-eared bat (*Myotisbocagii*), and has been implicated in sporadic cases of rabies in humans, underscoring the need for surveillance and monitoring of this lyssa virus (Johnson et al. 2006).

3.5. EUROPEAN BAT LYSSA VIRUSES (EBLV)

European Bat Lyssa viruses (EBLV) consist of different strains found in bat species in Europe, posing potential risks to humans (Fooks et al. 2003). EBLV-1 and EBLV-2 are the two primary strains identified, with EBLV-1 related to serotine bats (*Eptesicusserotinus*) and EBLV-2 related to Daubenton's bats *(Myotisdaubentonii*) (Picard-Meyeret al. 2011). These strains have been responsible for a number of bat-associated rabies cases in Europe.

3.6. GEOGRAPHIC DISTRIBUTION AND HOST RANGE

3.6.1. LYSSA VIRUS DISTRIBUTION PATTERNS

Lyssa viruses exhibit varying geographic distribution patterns, which impact their prevalence and occurrence in different regions. This section explores the global distribution of lyssa viruses and associated factors. Streickeret al. (2013) conducted a study on the global distribution of bat-associated lyssa viruses, revealing regional differences in lyssa virus diversity and prevalence.

3.7. GLOBAL DISTRIBUTION OF LYSSA VIRUSES

Lyssa viruses have a worldwide distribution, with varying prevalence across continents,countries, and regions. Africa, known for its high prevalence of lyssa viruses, hosts several species, including Rabies

lyssa virus (RABV), Lagos Bat Virus (LBV), Mokola Virus (MOKV), and Duvenhage Virus (DUVV) (Marston et al.2012). In Asia, Rabies lyssa virus is the most common and widespread, with countries like India, Thailand, and China reporting a high number of human cases annually (Hu et al. 2013). Europe is of concern due to the presence of European Bat Lyssa viruses (EBLV) (McElhinneyet al. 2013), while North and South America have a significant burden of rabies cases, primarily transmitted by wildlife species (Freire de Carvalhoet al.2017).

3.8. FACTORS INFLUENCING DISTRIBUTION

Various factors influence the distribution of lyssa viruses. Bats, particularly insectivorous species, serve as important reservoirs for lyssa viruses, contributing to their prevalence in different regions (McElhinneyet al. 2013). Factors such as bat species diversity, human-animal interactions, and vaccination coverage can impact the transmission dynamics and regional prevalence of lyssa viruses (Hu et al.2013).

3.9. PREVALENCE AND CHALLENGES

The prevalence of lyssa viruses varies within regions due to local ecology, population density of reservoir hosts, and control measures implemented. Inadequate vaccination coverage, limited access to post-exposure prophylaxis, and inadequate surveillance systems contribute to the persistence of lyssa virus transmission. Socioeconomic factors, cultural practices and wildlife trade also play a role in the prevalence and challenges associated with lyssa viruses (Freire de Carvalhoet al. 2017).

3.10. TRANSMISSION OF LYSSA VIRUS

The biting of a rabid animal can transmit rabies and also by licking the rabid animal because saliva may also contain the lyssa virus. Corneal transmission from man to man is also seen. In modern days air born infection is also prevailing. In non-bitingtransmission category, the virus can be transmitted between laboratories workers. Rabies can also be transmitted by abrasion or open wounds that are exposed to the saliva or potentially hazardous material of a rabid animal (Dutta et al. 1992).

3.11. VIRAL REPLICATION:

3.11.1. THE REPLICATIVE CYCLE OF LYSSA VIRUS

The replication of the lyssa virus is just similar to that of other negative-stranded RNA viruses.

3.11.2. ATTACHMENT AND ENTRY INTO HOST CELL

The lyssa virus attaches to the host cell membrane via the G protein through the phenomenon of adsorption. After that, the lyssa virus creeps into the cytoplasm either by pinocytosis or fusion mechanism.

3.11.3. UNCOATING AND RELEASE OF VIRAL GENETIC MATERIAL

Uncoiling occurs within the cytoplasm, and genetic material is released, whereas the outer portion of the virus remains outside. After uncoating, the viral genome takes control of the host cell.

3.11.4. VIRAL GENOME REPLICATION

The core initiates the primary transcription of the five complementary monocistronic mRNAs by using virion RNA-dependent RNA polymerase. Each RNA is then translated to an individual protein.

3.11.5. EXPRESSION OF VIRAL PROTEINS

After viral proteins have been synthesized, replication of the genomic RNA continues with the synthesis of full-length, positive stranded RNA, which acts as a template for the production of progeny negative-stranded RNA.

3.11.6. ASSEMBLY AND MATURATION OF NEW VIRAL PARTICLES

After Renovo synthesis of viral genome and proteins, which can be post transcriptionally modified, viral proteins are packaged with newly synthesized viral genome into new visions that are ready to release from host cell. This process cans also refer to as maturation (Marston et al. 2018). All the steps have been shown in Fig. 2.

4. PATHOGENESIS OF LYSSA VIRUS IN THE HOST

4.1. PRIMARY REPLICATION IN LOCAL TISSUES

The virus first spreads from the bite site to the striated muscle spindle receptor of the wound, where it builds up and reproduces before spreading to the adjacent peripheral neurons. Peripheral nerve invasion typically occurs to three days after a local wound, while others believe the virus may remain at the invasion site for up to 2 weeks (Kuzmin and Tordo2012).

4.2. DISSEMINATION TO THE CENTRAL NERVOUS SYSTEM

At a rate of roughly 3 mm/h, the virus disseminates centripetally along the axonal plasma of the peripheral nerve. The virus multiplies after it enters the dorsal root ganglion before spreading to the spinal cord and the rest of the central nervous system, mainly infecting neurons in the brain and cerebellum (Murphy 1977)

4.3. NEURO INVASION AND SPREAD WITHIN CNS

The virus uses the endosomal transport system (endocytosis) to connect to surface cellular receptors and begin infection. The uncoating of virus particles and the release of helical RNP into the cytosol are caused by the low pH of the endosome, which also causes a process of membrane fusion. The P-L complex transcribes the viral genome in the following phase, resulting in the production of five positive-strand monocistronic mRNAs, followed by the translation of five viral proteins. Positive-strand replicative RNA (anti-genome), which serves as a template for creating a negative strand RNA genome, is created when the RNA polymerase activity shifts from transcription to replication. In order to create RNP, the produced viral RNA is subsequently packed with the N-P complex, and L. Then M joins the RNP complex to condense (Baloul and Lafon 2003). All the steps of pathogenesis are shown in the Fig. 3.

4.4. PATHOLOGICAL CHANGES IN THE BRAIN AND NERVOUS SYSTEM

Numerous variables, many of which are yet unknown, influence the clinical signs of rabies, which can take many different forms. However, the presentation of various clinical signs varies depending on

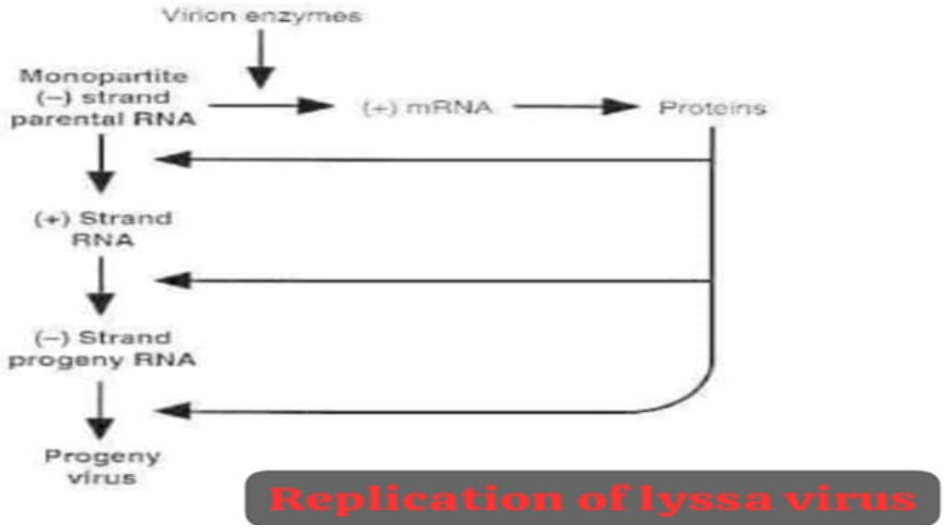

Fig. 2: Replication of lyssa virus

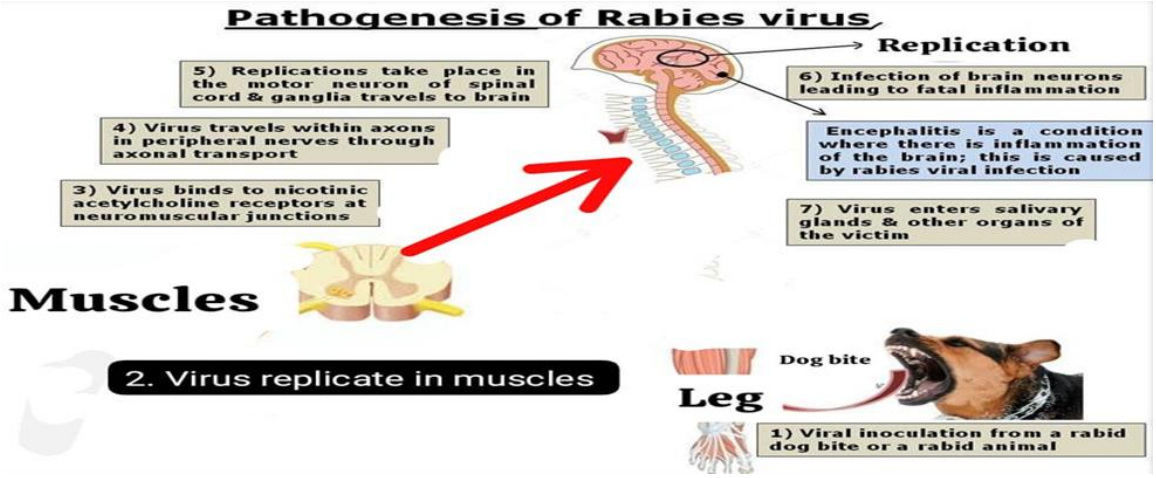

Fig. 3: Pathogenesis of lyssa virus.

depending on the lyssa virus species or RABV strain. For instance, dog strains of the RABV more typically exhibit classic hydrophobia and aerophobia, while bat strains more frequently exhibit tremors and involuntary jerking/twitching (myoclonus). Additionally, compared to dog rabies exposures, exposure to bat rabies was more likely to present with symptoms that were localized to the wound. Encephalitic (or classical or angry) and paralytic rabies, also called dump rabies, are the two types of rabies that can occur. In around80 % of patients encephalitic form of rabies is effective; of these, between 50 and 80% along with the typical signs of rabies, such as water phobia and fear of air. The remaining indications are specific like encephalitic illnesses, particularly in people of Africa, where dominant conditions like cerebral malaria can lead to rabies misdiagnosis. Unlike paralytic rabies, which is pronounced in the early days of illness, muscle weakness can be seen in the second form, encephalitic rabies often leads to severe coma, paralysis, and death, which may occur cause many organs get failed to work properly. Initially, it was believed that the symptoms of rabies were

brought on by widespread neuronal cell death; however, neuronal apoptosis is only induced by infections with strains with low pathogenicity. Instead, dysfunctional neuronal cells are assumed to be the cause of symptoms, which is in part brought on by increased NO synthesis by inducible nitric oxide synthase (NOS) in neurons and macrophages. Axonal swelling also occurs due to malfunctioning of mitochondria. This pathology is linked to the symptoms appearing, and it explains the symptoms of encephalitis (Hicks et al. 2013).

4.5. IMMUNE RESPONSE

4.5.1. INNATE IMMUNE RESPONSE

NF-kB transcription factors are involved in many cellular responses. Viral infections activate NF-κB that expresses antiviral cytokines. One of the members of NF-κB family named RelAp43 that expresses the genes involved in innate immune response. RelAp43 induces the expression of HIAP1, IRF1, and IFN-β. RelAp43 is also seen to be targeted by the matrix protein of lyssa virus (but not vaccine strains), which inhibits the NF-kB pathway, resulting a virulence factor (Luco et al. 2012).

To study the innate immune response within the brain to the lyssa virus, the mouse was subjected to infection. Transcript levels associated with innate response includingSTAT1, including IFN-c, tumors necrosis factor alpha, interleukin 6(IL-6), IL-1b, T-cell growth factor b and Toll-like receptors (TLRs), and the antiviral protein Mx1 were seen increased in the brains of mice (Koraka et al. 2018).

Type 1 IFNs were selected as the critical role in the development of the antiviral state chosen selected as a marker for the inflammatory response to viral infection in the CNSand Mx1 was selected as an IFN-inducible transcript with known antiviral properties for negative-strand RNA virus. Mice being inoculated were sacrificed, and their brains were removed to study disease. Transcripts of lyssa virus and host were analyzed by end-point PCR and quantitative PCR, respectively (Johnson et al. 2006). Amplifications were performed by a thermal cycler using an annealing temperature of 50 degree calcius(Johnson et al. 2006). It was observed that laboratory-adaptive viruses exhibit intensive inflammation and necrosis. Studies showed that the B2C variant stimulates gene expression of innate immunity (Wang et al. 2005).

5. ADAPTIVE IMMUNE RESPONSE

Investigations show that current rabies vaccines provide immunity against the lyssa virus classified within phyllogroup I. However, it does not give any Protection against phyllogroup II or any other variant. All these rabies vaccines comprise inactivated preparations of live attenuated classical rabies virus strains (Evans et al. 2012).

BALB/c mice were infected with lyssa virus through a peripheral route to study the responsiveness of T-cells (RTC). Two types of virus could be classified after the progression of infection.

1) Pathogenic virus
2) Non-pathogenic virus

The studies revealed that infection with pathogenic lyssa virus resulted in loss of RTC in subjected mice after antigen activation but not after polyclonal activation (Perrin et al. 1996).

5.1. CONTROL OF INFECTION BY ADAPTIVE IMMUNE RESPONSE

According to a study, mice infected with lyssaviruswere subjected to anti-lyssa virus human monoclonal antibody (mAb), F11, to demonstrate the efficacy of immunotherapy in subjected mice. The studies

revealed that even a single dose of F11 therapy can stimulate an adaptive response (T-cell dependent) that is highly effective against established CNS infection caused by virus(Huaman et al. 2022).

5.2. IMMUNE EVASION STRATEGIES EMPLOYED BY LYSSAVIRUS

Type I interferon are expressed as a host response to viral infection in humans, activating intracellular signaling (Wiltzer et al. 2012). Lyssa virus P protein plays an important role in the replication of the virus and immune evasion, which act as an antagonist of IFN 1 that targets signal transducers and activators of transcription (STATs). Phosphorylation of the C-terminal of tyrosine and cytokines activates STATs, which leads to the formation of hetero dimmers which accumulate within the nucleus. P protein directly binds to STAT 1 interacting C-terminal domain, hence binding strongly with tyrosine phosphorylated STAT hetero dimmers inhibiting the accumulation in the nucleus thus, affecting cytoplasm localization of complex. This inhibition mechanism appears to be critical in pathogenic RABV infection and progression. However, this detailed mechanism of inhibition of IFN production and pathogenicity of thelyssa virus cannot be completely understood (Harrison et al. 2020).

5.3. CLINICAL MANIFESTATIONS OF LYSSA VIRUS

These include headache, fatigue and fever. Then progresses to paralysis, convulsions and death within 1 to 2 weeks. Symptoms start from a few days to several years after contact with virus. In 1996, a 39-year-old female carried weakness of one arm followed by nervous symptoms, bulbar palsy and death within twenty-one days (kazachinskaia et al. 2022). In 1998, a female developed nervous illness, to which she ultimately succumbs. In 2018 a boy developed fever, anorexia, abdominal pain, distress, abnormal and aggressive behavior followed muscle spasms.

5.4. INCUBATION PERIOD AND INITIAL SYMPTOMS

According to WHO, the incubation period of lyssa virus is about 2 to 3 months but may vary from 1 week to 1 year depending upon the site of virus entry and viral load Initial symptoms like fever, pain, unexplained tingling, prickling and burning sensations (Poleshchuket al. 2023).

5.5. PROGRESSIVE NEUROLOGICAL SYMPTOMS OF LYSSA VIRUS

According to Charles E. Rupprecht, Neurological signs include nervousness, anorexia, irritability, ataxia, hyper excitability etc. There are two forms of rabies:

5.5.1. FURIOUS RABIES

Results in excited behavior, hydrophobia, aerophobia, ataxia, hyperactivity, etc. Death occurs in a few days because of cardio respiratory arrest (MSD Manual)

5.5.2. PARALYTIC RABIES

Presents about 20% in humans. This is less dramatic and usually longer than furious. Muscle becomes paralyzed. A coma develops, and death occurs (Hemachudha et al. 2005).

5.6. DIVERSE CLINICAL PRESENTATIONS IN DIFFERENT HOSTS

Bats are recognized as reservoir hosts which cross barriers to infect humans and other mammals. Bats are found everywhere in the world except Antarctica.New lyssa virus genome from the Lesser Mouse-eared bat (*Myotisblythi*), Kyrgyzstan They are emerging infectious Diseases. When bats are kept at low temperature, a virus with high titer is obtained associated with lyssa virus. Incarnivores' immune response is delayed until the centrifugal phase due to lymphocytic infiltration in infected tissues. Due to this, lymphocytic encephalitis is reported (Begeman et al. 1985).

5.7. DIAGNOSIS AND LABORATORY TECHNIQUES FOR LYSSA VIRUS

In rabies, lyssa virus diagnosis cannot be made during the incubation phase. As this is very common disease, now, physicians, doctors and patients less apart to diagnosis with laboratory techniques. The useful behavior of physicians for diagnosis is based on clinical signs and symptoms. After the appearance of clinical signs, mortality is 100%. The most challenging clinical signs are high protein concentration, abnormal cerebrospinal fluid, normal glucose level, and high T2 signaling (Dacheux et al. 2016).

5.8. SEROLOGICAL ASSAYS

5.8.1. DIRECT FLUORESCENT ANTIBODY TEST (DFAT)

This is a gold standard antibody test, highly sensitive and specific. For confirmation, a mouse inoculation test is performed. In this technique, the sample is collected from brain cells, i.e., cerebellum, brain stem cells and cortex sometime, skin biopsy is done. Take a slide and air dry it for 15-30 min at room temperature. Prepare positive control slides of rabies affected animal and negative control slides of the healthy animal. At the same time, prepare test slides as well. Hold it for 2 min; now, fix it with chilled acetone at -20°c for 30 min. Air dry it and incubate at 37°c for 30 minutes.Immerse the slide in PBS and air dry. Add mounting media as Fluoresce in isothiocyanate. Place the cover slip and observe under the fluorescent microscope at 400X. Lyssa virus antigen appears as fluorescent apple green intra cytoplasm inclusions for positive slides (European Union Reference Laboratory for Rabies 2021).

5.9. MOLECULAR METHODS FOR VIRUS DETECTION

5.9.1. RT-qPCR

To improve relevant specificity and sensitivity, a highly modified technique is real time reverse transcription PCR for Lyssa virus detection. The protocol is based on two types of reaction: (1) first reaction is probe based (TaqMan) real time reverse transcription PCR for rabies species as (Pan-RABRT-qPCR). (2) Second reaction uses a dye (SYBR GREEN) for other lyssa virus species (Pan-lyssa RT-qPCR).The collection sites for this test are brain tissues, saliva or CSF. In humans, lyssa virus detection (rabies), the best site is saliva as brain tissues or nerve cells sloughed off in CSF, which may give false positive PCR results. This method is more specific and less expensive than DFAT. (Biswal et al. 2007).

5.10. HISTOPATHOLOGICAL EXAMINATION OF LYSSA VIRUS

For immune histochemistry, sample is taken from hippocampus, mid-brain, thalamus etc. Tissues are first deparaffinised, fixed with 3% hydrogen peroxide, washed with water and exposed to buffer solution for 10

min and block solution for 7 min. Incubate for 30 min at 37°C. Stain the slide with Mayer's hematoxylin and cover it with cover slip for observation. The test sample contains intracytoplasmic inclusions as Negribodies' labelled, oval homogenous structure (Hooper et al. 1999).

5.11. PREVENTION & TREATMENT

Management and caring for animal is the central stone of any modern program for the prevention and control of rabies. However, with proportionally few exceptional cases, separating alone has not led to productive control of rabies (Nigg and Walker 2009).

5.12. CAN RABIES BE ELIMINATED?

Rabies, acute continuous encephalitis, is a former zoonosis. Society must recollect that despite the current identification of other important emerging infectious diseases, none surpass the case fatality rate of rabies. Given the clear significance of rabies in public health, agriculture and conservational biology, considerable international development must pursue amplified public consciousness, human rabies prevention, wildlife rabies control, and canine rabies cancellation with refreshed, concerted vigor (Maclnnes et al. 2001).

5.13. PREVENTION IN MAN

Man is infected by the bite of a domestic rabid animal which put on him, or of violent wild animals (including bats) which inexcusably attack him. So, rabies in man can be prevented by keeping themselves safe from rabid animals by seeing the clinical signs of animals. Bats should be avoided from coming into the homes (Plotkin and Clark 1971).

5.14. TREATMENT

Rabies is the identically lethal viral encephalitis that causes 30,000 to 70,000 deaths worldwide per year.

5.15. PRE-EXPOSURE PROPHYLAXIS

Two more IM doses of vaccine must be given to the person having the possible rabies exposure; the preliminary dose should be administered straight away following the liability and the 2ndshould be administered three days later (Damanet et al. 2023).

5.16. POST-EXPOSURE TREATMENT

To reduce the chance of bacterial infection, the wound should be cleaned with water and soap considerably. A solution of Povidoneor ethyl alcohol 70% can also be used for this purpose to control the viral infection Behavioral abnormalities must be checked and noticed for at least ten days in the animal having the least risk of rabies. During these ten days observational period, at the first sign of rabies, treatment with RIG (Rabies Immune Globulins) and rabies vaccine should be done. 20IU/KG body weight is the dose criteria for RIG. Pain and soreness at the site of infection are some common side effects of the RIG. This RIG is used in passive vaccination.

5.16.1. ACTIVE VACCINATION

Almost two inactivated virus vaccines are available now.

1. Human diploid cell rabies vaccine (HDCV). Produced in human diploid cell culture.

Purified chick embryo cell vaccine (PCECV). Produced in chicken embryo cell culture (Jackson 2020).

5.17. CONCLUSION

The lyssa virus is one of the most prevailing fatal viruses spread by biting a rabid animal or human. So, public health departments should work with the government on local, national, and international level to eradicate this fatal condition. By understanding the transmission, pathogenesis of the Lyssa virus one can be able to make strategies to overcome its outbreaks, and treatments can be effective. By having enough knowledge about the pathogenesis of rabies from this chapter, research institute get huge benefits and can make remarkable achievements in devising the way for the permanent control and eradication of rabies. By having the proper knowledge of pathogenesis of the rabies, one can differentiate rabies from meningitis and encephalitis.The most prominent disease caused by the Lyssa virus is rabies, which is a neurological disease and thousands of deaths due to rabies are recorded per year. Louis Pasture was the first scientist to develop the vaccine against rabies. Simply by understanding the pathogenesis of rabies, we will be able to mitigate that havoc disease. With enough knowledge of the pathogenesis of lyssa fever, one can be able to know the chain of events that occurs during disease development and progression. By knowing the pathogenesis pattern veterinarian or researcher can find the perfect treatment and prophylaxis at the respective stage. Pathogenesis begins with the transmission, so by blocking the transmission routes and inhibiting or deactivating cell surface receptors (alpha - DG), the progressing of the rabid fever can be blocked.

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