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Review Article

Rabies: Diagnostic, Treatment, and Prevention

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ABSTRACT

Rabies is a neurological disease with fatal impacts because it has a high mortality rate. Animals, primarily dogs, mediate the spread of rabies. Clinical findings of rabies are divided into two categories: classic rabies (furious type) and paralytic type. Furious rabies has many cardinal features, such as fluctuating consciousness, aerophobia or hydrophobia, inspiratory spasm, and autonomic dysfunction. Ascending paralysis with a lower motor neuron lesion is the initial sign of paralytic rabies. The rabies virus invades and lives in neurons. It is virulent. Besides clinical findings, the diagnostic approach can involve radiology, microbiology, and histopathology. There are not only symptomatic treatments for rabies patients but also vaccines, immunoglobulin, and antivirals to decrease the progressivity of the disease. Vaccination programs and animal control have become essential in reducing rabies cases in Indonesia.

1. INTRODUCTION

Rabies is a zoonotic disease caused by a viral infection. It is categorized as a preventable disease with vaccination. Rabies has become a neglected tropical disease, evolving in more than 150 countries.(1) Up until the 21st century, rabies has remained a fatal disease and a threat to public health. In cases without adequate treatment, the progression of the disease increases to encephalomyelitis, with a fatal impact on the patient's death. There is an obstacle to evaluating rabies cases due to the low implementation of surveillance and limited laboratory infrastructure, and it continoues to be taboo in a few cultures and social environments.(2) This review article aims to understand the holistic approach in rabies cases so the clinician can treat the patients well and support the rabies eradication program in Indonesia.

2. EPIDEMIOLOGY

Rabies cases in Asia, especially in developing countries, are still a concern. The predominant cases are in Bangladesh, India, Nepal, Myanmar, Bhutan, Thailand, and Indonesia.[3] A systematic review by Jane Ling showed that rabies cases in Southeast Asia, such as Vietnam, Indonesia, and Thailand, are still higher than in others. Those countries are categorized as having endemic rabies. Many wild dogs hang around, and unvaccinated dogs are a risk factor for increasing rabies cases. Low vaccination rates in risk categories escalated the number of cases. The climate is another risk factor for rabies infection. It is caused by a warm climate that makes the animals active, and citizens wear loose clothes that expose their skin and increase the risk of being bitten by dogs.[4]

The high fatality rate reaches 100% of patients dying of rabies infection. The estimated global mortality rate is reaching 59,000 human deaths annually. Asia has 59.6% of deaths, followed by Africa (36.4%) and the Americas (less than 0.05%). There are two studies reporting mortality cases in Southeast Asian countries.[4] 463 people died of furious rabies without laboratory confirmation in the Philippines,[5] and 104 fatalities (96 cases had a history of dog bites) occurred in Indonesia.[6] The availability of vaccines was scarce in rural areas. Moreover, immunoglobulin was hard to find because of the high mortality rate of the rabies virus.[4]

From 104 patients in an epidemiological study from Susilawathi in Bali, the mean age was 36.6 years (3–84 years and a standard deviation of 20.7). As many as 56.7% of cases happened in males. The highest cases were reported in Karangasem Regency (28.8%), Buleleng (19.2%), and Tabanan (17.3%). Based on bitten areas, lower extremities (59.3%), upper extremities (37.2%), and head neck (3.5%) Approximately 80.8% of patients were not doing wound care, 10.6% washed their bite lesions, and only 5.8% took the patients to the hospital at the time of incidence.[6]

Another epidemiological study about rabies molecular structure from Susetya confirmed that all isolated viruses in Indonesia were categorized as genotype 1 Lyssavirus, the classical genotype of the rabies virus. Phylogenetic analysis shows three phylogroups of rabies in Indonesia: Indonesia (ID) 1 (consisting of lineages Sumatra Central (SC) 1, SC2, SC3, and Sumatra (ST)) were isolated in Sumatra; ID2 (consisting of lineage Java (JA)) was isolated in Java; and ID3 (consisting of lineages Kalimantan-Sulawesi (KS) and Sulawesi-Flores (SF)) were isolated from an east region in Indonesia such as Kalimantan, Sulawesi, and Flores. The animals infected in Indonesia, besides dogs, are cats, cows, deer, monkeys, and tigers.[7]

3. ETIOLOGY

The rabies virus causes acute infection and is a taxonomically ordered mononegavirales. Rabies virus is a single-stranded, negative-sense ribonucleic acid (RNA) with the family Rhabdoviridae and genus Lyssavirus.[8,9] Alpharhabdovirinae, Betarhabdovirinae, and Gammarhabdovirinae are the three major subfamilies of the Rhabdoviridae family. Only the subfamily Alpharhabdovirinae can infect both vertebrates and invertebrates. Rhabdoviruses, including Lyssavirus, are spread from mammal to mammal. Human illnesses are linked to several viruses of the Alpharhabdovirinae subfamily from the genera Lyssavirus, Ledantevirus, Vesiculovirus, and Tibrovirus; however, non-lyssavirus species are infrequently seen in humans.[10] Viral virions are

enveloped by the host cell and shaped like a bullet with a length of 130–250 nm and a 60–100 nm diameter. It has two functional units: the inner side with a nucleocapsid core includes genomic RNA, and the outer side has two lipid layers with protruding spikes from viral glycoprotein.[11] The small viral genome (~12 kb) encoded five proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and polymerase (L) (**Figure 1**).[12]

Viral proteins have many functions. Protein N is a primary component for covering the viral genome from cellular RNAse activities and interacts with proteins L and P in the transcription and replication processes. Protein P, a non-catalysis polymerase cofactor, helps position protein L compatible with N-RNA molding and becomes a chaperone in protein N synthesis. Protein P interacts with the host cellular transport system. Protein M is bound to the nucleocapsid and the protein G cytoplasmic domain and facilitates the budding process. Protein G is a viral component on the virion surface. It mediates the host cell receptor's binding, induces endocytosis, and fuses the virus with the endosomal membrane. As only one external component, protein G acts by inducing the formation of virus-neutralizing antibodies (VNA). Cells are eliciting an immune response. Protein L has many domains, acts in the transcript, and replicates the genome.[11]

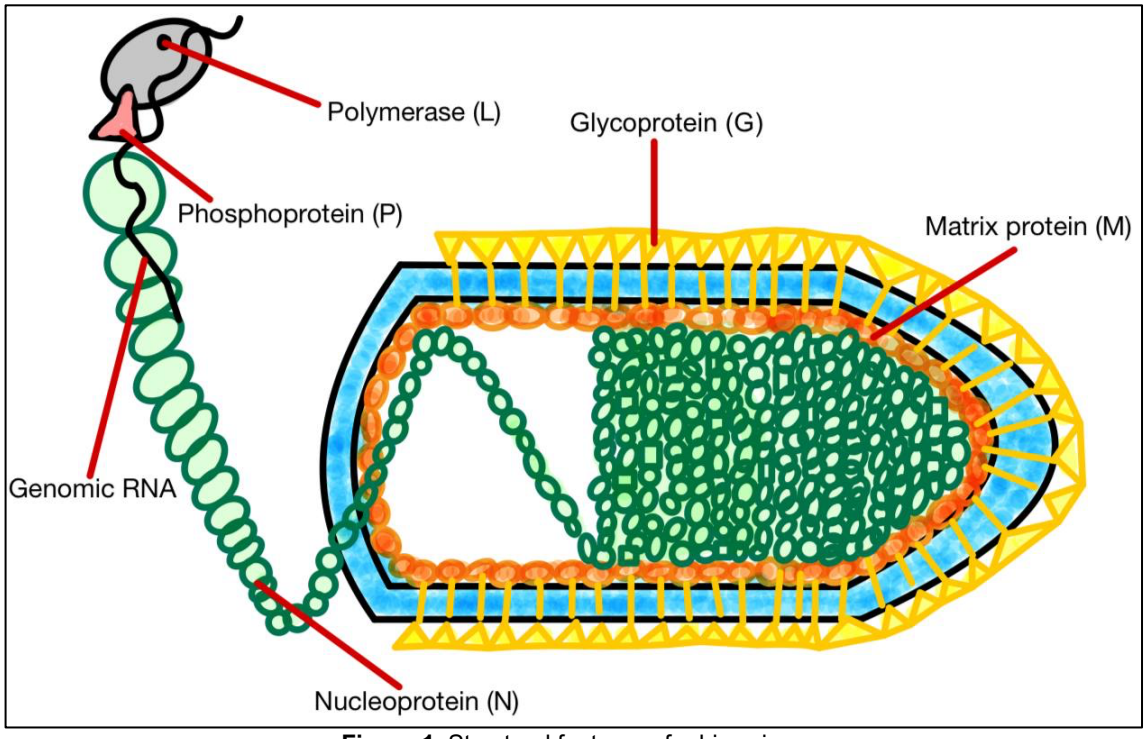

Figure 1. Structural features of rabies virus

The Rabies virus cannot live outside the host cell and becomes inactive when exposed to sunlight, heat, and dry conditions. It has seven genotypes: classic rabies virus (genotype 1), Lagos bat virus (genotype 2), Mokola virus (genotype 3), Duvenhage virus (genotype 4), European bat Lyssavirus (genotype 5 and genotype 6), and Australian bat Lyssavirus (genotype 7).[3] The Lyssavirus genus contains the rabies virus, a type of species that mostly affects humans worldwide. Other viral species, including European bat Lyssavirus-1 and 2, spread throughout Europe, while Duvenhage virus and Mokola virus infect Africa, and Australian bat Lyssavirus is only endemic in

Australia.[10] Most rabies viruses are transmitted from saliva from the bite or scratch of wild animals.[8] Saepulloh's study in analyzing genetic mapping of the rabies virus showed that the isolated rabies virus in Indonesia has a genetic relationship with the rabies virus from China. Veterinarians (from the United States) use the rabies vaccine, which has a closer genetic relationship with an isolated virus in Europe. Nevertheless, homolog levels with the isolate virus in Indonesia reach 95% and are quite effective if used in Indonesia and China.[13] Other vectors are bats, and rabies cases are less than 10% in America and Canada, and in the last 20 years, the rabies variant from that country has become a leading cause of death in humans.[9]

4. CLINICAL FINDINGS

Initial complaints in rabies cases are usually pain, tingling, or itchiness in the bitten area. It causes viral replication localized in the dorsal root ganglia. Clinical findings are divided into encephalitis (furious type) and paralysis. The difference is that encephalitis (furious) type manifestations are hypersalivation, agitation, and hydrophobia, whereas the paralytic type has muscle weakness. Both of them will end in coma and death. However, the life duration of the paralytic type is longer than that of the furious type.[2] Typical rabies symptoms are aggression, anemophobia, hydrophobia, and progressive paralysis. Early symptoms of rabies are atypical findings such as flu, fever, headache, nausea, weakness, and decreased appetite. There are rare symptoms, such as abnormal sexual behavior, including frequent ejaculation, hypersexuality, and priapism. Abnormal sexual behavior is often misdiagnosed with other diagnoses. Abnormal sexual pathogenesis has not been completely understood yet. Viral invasion of the lumbosacral segment causes nerve irritation that induces erection in males. Conduction to smooth muscle in a ductus deferens, seminal vesicle, prostate, and ischiocavernosus muscle and getting through the hypogastric nerve and sympathetic nerve in the hypogastric plexus cause rhythmic contraction in that muscle group. It causes ejaculation. The effect on women is hypersexuality.[14]

Susilawathi shows common symptoms in rabies infection are agitation (89.2%) and confusion (83.3%), while autonomic dysfunction is hydrophobia (93.1%), hypersalivation (88.2%), dyspnea (74.5%), aerophobia (73.1%), photophobia (29.8%), and piloerection (4.8%). Other symptoms are fever (18.2%), convulsions (15.4%), and muscle fasciculation (3.8%). It can be cranial nerve involvement, such as ophthalmoplegia, facial weakness, and dysphagia, in 2.9% of patients. In rabies cases with paralytic type, there are many symptoms, such as urinary incontinence (27.5%), flaccid paralysis (21%), and abdominal discomfort (10.8%). Acute conditions end with sudden death or progressivity of coma with ends of death.[6]

A retrospective study from 2006–2015 by Guzman reports the clinical manifestations of rabies patients in Manila. Prodromal symptoms are pain sensation, itch, or numbness in the bitten area, fever (≥37^{o}C), and nausea or vomiting. Acute neurological conditions include restlessness, confusion, agitation, and behavioral changes, while typical symptoms include hydrophobia and aerophobia. Other clinical findings, such as dyspnea, hypersalivation, and photophobia, could occur. This study assesses the incubation period, and there are 30-90 days (42.1%), ≤30 days (22.7%), and more than one year (approximately 10% cases). Most of the patients were

dead within 48 hours of treatment. Only 2.4% lived more than 72 hours (a maximum of 163 hours).[5]

5. PATHOGENESIS AND PATHOPHYSIOLOGY

The main characteristics of the rabies virus are neuroinvasiveness, neurotropism (the potency of the virus to invade and live in neurons), and neurovirulence. Various influential factors in the pathogenicity of the rabies virus include rapid viral invasion, spreading from one cell to another, and viral replication. The primary role of protein G in the rabies virus is to intercede neuroinvasive mechanisms (including viral entry, outspread, and RNA synthesis).[15]

There are five different protein structures in the rabies virus, some of which are involved in immunological pathogenesis. A ribonucleoprotein (RNP) complex is made up of genomic RNA and the proteins N, P, and L. The RNP complex helps to induce $CD4^+$ T cells. It supports the role of the G protein by recognizing intrastructural antigens and promoting immunological memory and long-lasting immunity. The G protein is the only protein that contributes to the induction of rabies virus-neutralizing antibodies.[15]

Various incubation periods range from weeks to years. The incubation rate is usually 1-2 months. The long incubation duration may be caused by low-titer inocula and endogenous RNA-silencing mechanisms or microRNA that delayed viral replication in the muscle. Rabies virus causes high-titer inocula. It infects the motor endplate without replication in muscles; before, it was caused by the direct inoculation of nerves. That explains the short duration of rabies virus incubation.[16] After patients have been bitten, the G-protein receptor attaches the virus to target cells (such as myocytes and local motor and sensory nerves). Rabies virus is amplified in myocytes and macrophages. Afterward, it spreads to the central nervous system via muscle spindles of sensory nerves or neuromuscular junctions of motor nerves.[3]

Viruses get into peripheral nerves through bitten wounds. Viruses are exposed to terminal neurons and spread retrogradely until the spinal cord. Spread centripetally with cellular transport mechanisms. Transport to the cell body occurs throughout the microtubule, assisted by the dynein motor complex. Viral replication reaches the cell body, which transports anterogradely with the kinesin motor complex. From the spinal cord, the virus spreads to many areas in the brain (such as the cerebral cortex, cerebellum, diencephalon, midbrain, pons, and medulla oblongata). It passes the dorsal column to the cerebral cortex and synapses in the dorsal column nuclei (medulla oblongata) and thalamus (diencephalon). The other pathway is from the spinothalamic tract (to the cerebral cortex, with synapses in the thalamus and dorsal horn of the spinal cord), the spinocerebellar tract (to the cerebellum), and the corticospinal tract (to the cerebral cortex, with synapses in the ventral horn of the spinal cord).[17] It spreads from neuron to neuron via the p75 neurotrophin receptor (p75NTR). Protein L manipulates the microtubule to help viral transport and protein. M increases transcription and viral replication via the depolymerase process in the microtubule. Retrograde transports approximately 50–100 mm per day. Anterograde spreading does not have a precise mechanism. It spreads to the salivary gland through the terminal axon. Rabies virus spreads to peripheral (including non-neuronal organs) anterogradely (**Figure 2**).[18]

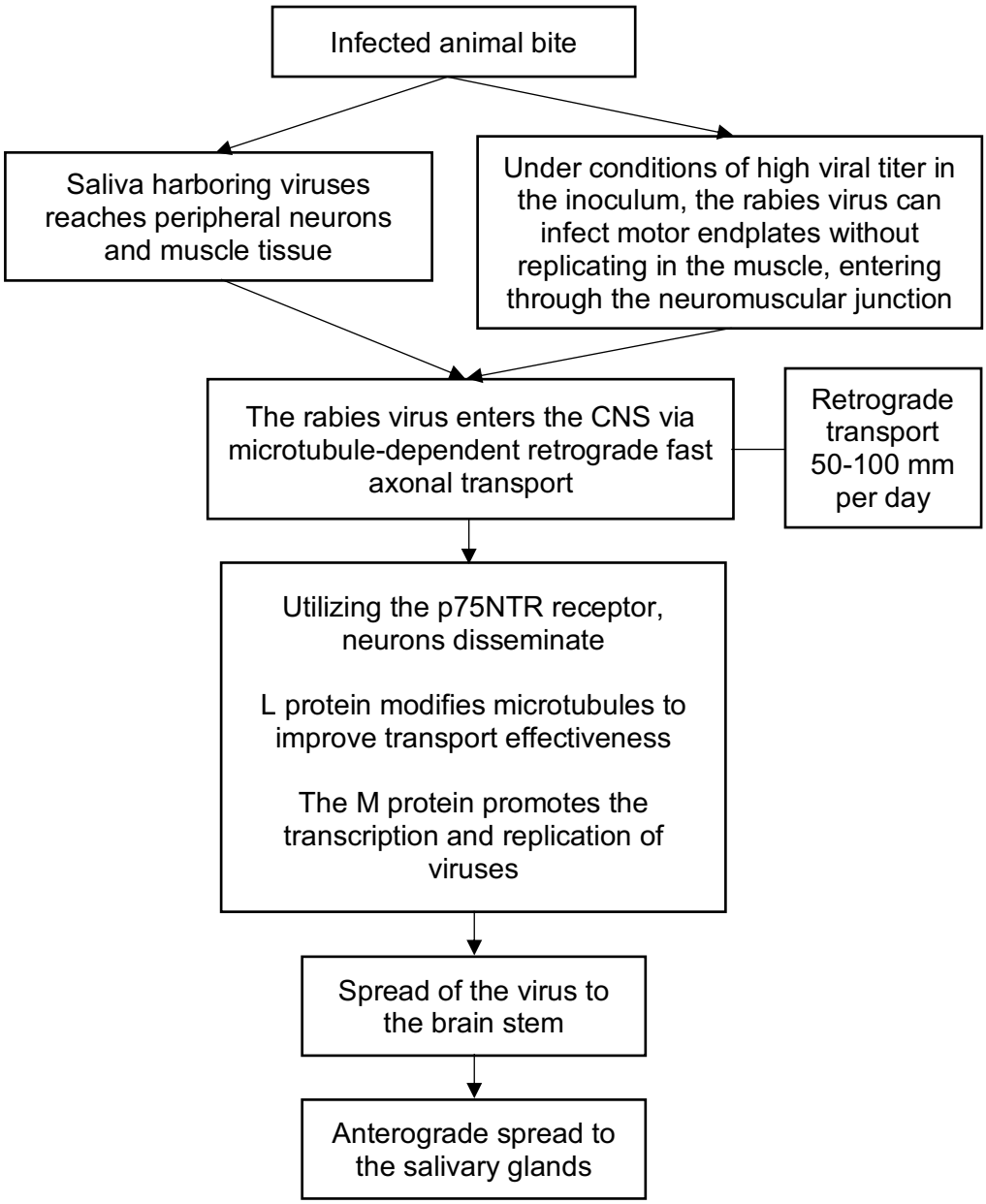

Figure 2. Diagram illustrating the pathogenesis and pathophysiology of rabies virus infection

The clinical manifestations of rabies are divided into furious and paralytic forms, with a ratio of cases of furious and paralytic rabies of 3:1. The mechanism that differentiates the two clinical conditions is still puzzling. On postmortem examination, no differences were found in the distribution of rabies virus antigens or differences in the degree of inflammation between the two clinical types. In cases of furious-type rabies, dysfunction of the anterior horn cells of the spinal cord can be assessed using electrophysiological examination. The central chromatolysis can be assessed using a postmortem examination. Meanwhile, in the paralytic type of rabies, peripheral nerve dysfunction, axonopathy, or myelinopathy play a greater role in the occurrence of paralysis.[19]

6. DIAGNOSTIC APPROACH

Laboratory findings have been used long ago as diagnostics in rabies cases. Adelchi Negri found Negri bodies in 1903. Histopathological findings in infected neurons have been known as viral particles. "Negri bodies," as intracytoplasmic inclusion bodies specifically for rabies encephalitis. The method to examine Negri bodies is Seller's technique, but it is insensitive and needs fresh specimens. Compared with the immunological method, histopathological findings are less sensitive in rabies diagnosis.[20] WHO generally divides laboratory findings into two categories: antemortem and postmortem. Antemortem findings are from the detection of RNA viruses (RT-PCR/reverse transcriptase polymerase chain reaction technique). The samples are from saliva, nuchal skin and hair follicles, cerebrospinal fluid, and antibody anti-rabies examination. The antibody examination techniques are the rapid fluorescent focus inhibition test (RFFIT), the fluorescent antibody virus neutralization test (FAVN), and the enzyme-linked immunosorbent assay (ELISA). That techniques use samples from cerebrospinal fluid and blood serum. A postmortem examination uses brain tissue. The gold standard in all rabies laboratories is the direct fluorescent antibody test (DFAT). It was susceptible and specific. If brain tissue is unavailable, RT-PCR can detect RNA viruses in cerebrospinal fluid, nuchal skin biopsy or hair follicles.[11] Another new technique for diagnosing human rabies is metagenomics next-generation sequencing (mNGS), which is an alternative option for detecting the rabies virus. In comparison with PCR, it does not use primers or specific amplification. Serial testing of cerebrospinal fluid and saliva increases the sensitivity of detecting the rabies virus. mNGS can be considered when conventional diagnostics are not available, there are uncertain clinical conditions, and it is applied in non-endemic areas; nevertheless, it still needs more research to diagnose human rabies.[21,22]

Brain imaging is another diagnostic approach that is used in rabies cases. Brain imaging can be used as an early diagnostic modality in rabies detection and is distinguished from other encephalitis. The typical clinical findings from the history and physical examination are that the patient is usually agitated. It means that imaging is rarely performed in rabies cases. A computed tomography (CT) scan and magnetic resonance imaging (MRI) can be done in rabies diagnostics. A CT scan showed a hypodense lesion without enhancement in the basal ganglia and symmetrical bilaterally. Other areas are the brainstem and hypothalamus, which are difficult to visualize in CT scans.[23] Few cases represent pontine hemorrhage, while diffuse cerebral edema is in follow-through.[24]

The MRI findings in the rabies case are as though they were clinical phases. The prodromal phase can be shown by brain and medulla spinalis involvement. Nevertheless, based on the case report, T2 hyperintensity with enhancement along the brachial plexus and spinal nerve roots can be found. It was reported that T2 had mild hyperintensity without enhancement in the spinal cord, temporal lobe cortices, or hippocampal gyri. In the acute phase, distinguishing between dog- or bat-bitten MRI findings is difficult. However, diffuse T2 hyperintensity in cerebral white matter was clearly shown in rabies of the furious type, which received immunoglobulin. The same condition is found in acute disseminated encephalomyelitis after being given post-exposure prophylaxis for rabies. In the comatose phase, the late phase showed a combination of hypoxia and ischemia. Blood-brain barrier leakage with moderate enhancement along the hypothalamus,

mammillary bodies, thalami, substantia nigra, brainstem, spinal cord, cranial nerve nuclei, and optic tract, with mild enhancement in the fifth and sixth cisternal cranial nerves. The enhancement was found in the intrathecal ventral and dorsal nerve roots.[25–27] Anatomic areas were involved in furious and paralytic-type differences. The furious type involves the ganglia basal, thalami, hypothalamus, limbic system, brainstem, and spinal cord, and the paralytic type involves the spinal cord and medulla.[24] Karande reports atypical rabies encephalitis and found an early brain MRI similar to acute disseminated encephalomyelitis (ADEM). It found T2/FLAIR hyperintensity in bilateral basal ganglia, thalami, and cerebellum. It involves diffuse, deep, and periventricle white matter. MRI findings showed gray matter atrophy in superficial and deep areas. It has a persistent hyperintensity of white matter in supra- and infratentorial areas.[28]

7. TREATMENTS

The rabies case almost had a fatal impact. Aggressive therapy needs intensive care and a high risk of treatment failure. The survival rate is influenced by some factors. There are viral etiologies (dogs bitten are more virulent than bats), types of viruses (encephalitis strains are more virulent than abortive strains), and host immune status. After exposure, the wound should be washed with soap and immunized. The patient must be silent in a dark area and get adequate oxygen and nutrition. Specific therapy can be given: rabies vaccine (active immunization), immunoglobulin (passive immunization), antivirus ribavirin, amantadine, interferon-α, and ketamine HCl. Minocycline and corticosteroids may worsen the disease.[29] Antiviral therapy and immunotherapy are essential therapies to deter viral propagation. Although in vitro antiviral therapy is promising, in vivo it has no significant clinical advantages yet. Immunotherapy as a monoclonal antibody has a specific target in a rabies virus protein, offering some promise in rabies therapy. However, the blood-brain barrier remains problematic as antiviral or immunotherapy penetrates the parenchymal brain.[30]

Since 1990, monoclonal antibodies have been created as a substitute for anti-rabies immunoglobulin in post-exposure prophylaxis regimens. These products include Rabishield® and Twinrab®. There is still more research needed on the monoclonal antibody dosage used in passive immunization. Anti-rabies immunotherapy has been created, and monoclonal antibodies have shown encouraging results as rabies prophylaxis. As a protocol for treating symptomatic rabies, the Milwaukee Protocol (coma induction and injection of ketamine and amantadine) still has not yielded conclusive results. It is anticipated that the novel therapeutic approach will use the neutralizing monoclonal antibody RVC20. The RVC58 will contribute to a decrease in viral load and a modulation of inflammation in the central nervous system. It is envisaged that these two monoclonal antibodies can be developed into a new paradigm in the treatment of rabies in humans. These two monoclonal antibodies have a therapeutic role in symptomatic rabies mice.[31,32]

Palliative management is needed in a rabies encephalomyelitis case. Treatment of dehydration, fever, anxiety, fear, agitation, restlessness, hypersecretion, seizures, and pain sensations as part of palliative management. Intravenous fluids include dextrose 5%, normal saline, or ringer lactate. Aspirin, acetaminophen, or ibuprofen can be given as antipyretics. In central hyperthermia, bromocriptine, amantadine, baclofen, and dantrolene can be given, but those medications are rarely found in developing countries.

Benzodiazepine (as diazepam and midazolam), haloperidol, and chlorpromazine can overcome the anxiety and agitation. Anti-muscarinic anticholinergic drugs, such as hyoscine hydrobromide (scopolamine), can reduce hypersecretion. For pain, it can be treated with opioids and strong analgesics such as morphine and fentanyl. The progress of the disease can cause other complications, such as cardiovascular, respiratory, gastrointestinal, endocrine, and coma.[33]

8. PREVENTIONS

Pre-exposure prophylaxis (PrEP) is given to high-risk groups, such as people working with high-risk rabies animals or traveling to endemic countries. The Advisory Committee on Immunization Practices (ACIP) recommends vaccines to prevent rabies disease in America, and that recommendation was renewed in May 2022. The new recommendations are: 1) the PrEP schedule has changed from 3 dosages to 2 dosages in 3 years of coverage; two dosages of human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) in days 0 and 7; 2) risk categories divided into five groups; 3) Revision of standard minimum antibody titer as a parameter for booster becomes 0,5 IU/mL; 4) Serial titer checking was recommended every two years before; now it changes to once checking (and booster is given if antibody titer is less than 0,5 IU/mL) or booster once; 5) There are PrEP clinical guidelines for immunosuppressed conditions and recommendations for vaccine effectiveness. Modern rabies vaccines are inactive and safe for all ages, including pregnant women and immunocompromised patients. However, ACIP recommends, if possible, delayed vaccination until the immunocompromised condition is handled or getting immunosuppressive medications. When the immunocompromised condition has not been handled yet, vaccination can be given with an antibody titer checked 2-4 weeks after two dosages. A low antibody titer suggested getting a booster. Moreover, after two booster dosages, low-titer antibodies need consultation for case-specific guidance.[34]

Post-exposure prophylaxis (PEP) is given as early as viral exposure, which becomes essential. There are many vaccination types: cell culture or embryonated egg-based vaccines (CCEEVs), such as purified chick embryo cell vaccine (PCECV), purified Vero cell rabies vaccine (PVRV), purified duck embryo vaccine (PDEV), and human diploid cell vaccine (HDCV). As a WHO recommendation, vaccines were injected intramuscularly or intradermally. PVRV and PCECV are used widely in developing countries. Two regimens from WHO are: 1) the Essen regimen with five dosages (1-1-1-1-1) on days 0, 3, 7, 14, and 28; and 2) the Zagreb regimen (2-0-1-0-1) on days 0, 7, and 21. The challenge in rabies vaccinations is the patient's compliance with receiving one month's dosage.[35] The Ministry of Health of the Republic of Indonesia uses PRPV or PCECV injected intramuscularly in the upper arm (deltoid muscle) or anterolateral thigh (in infants less than one year) with the Zagreb regimen. In bitten patients with complete vaccination before, if they bit less than three months after vaccination, no re-vaccination is needed. Between 3 - 12 months, one dose of vaccination is needed, and >12 months need re-vaccination with a total dosage.[36]

Though the anti-rabies vaccine is given as soon as possible after being bitten, it induces neutralizing antibodies with a seropositive titer ≥0,5 IU/mL after 7–14 days post-first dosage vaccine. Within that timeframe, third-category exposure patients need rabies immunoglobulin or anti-rabies serum. The serum aims to neutralize the virus in the bitten

area and save the patient. Two types of serum anti-rabies antibodies are equine rabies immunoglobulin (ERIG) and human rabies immunoglobulin (HRIG). HRIG has relatively low side effects because it uses homologous serum from humans, and ERIG uses heterologous serum from equine. A dose of HRIG is given on day 0, not more than 20 IU/kgBW. A cohort perspective study from Haradanhalli showed strong evidence for the clinical benefits and safety of third-category exposure. Side effects that may appear are pain in the injection area, itching, redness, and systemic effects such as fever, headache, and muscle ache.[37] The Ministry of Health of the Republic of Indonesia recommends that the HRIG dosage be 20 IU/kgBW, that it be infiltrated as much as possible around the wound, and that the remaining serum be injected intramuscularly on day 0. ERIG can be given at 40 IU/kgBW, and the remaining serum can be injected intramuscularly.[36]

In patients dead with rabies suspected, that is categorized as infectious but not "contagious" (either in the air or droplets). Many viruses are found in human tissues and body fluids, such as saliva and the central nervous system. However, the virus is not contained in the blood. Organ transplants from a dead body with rabies symptoms are not recommended.[38]

9. PROGNOSIS

The furious type, which did not get intensive treatment, and the unvaccinated patient will die in a few days, while the paralytic type can survive for a few weeks. Vaccination history before or after viral exposure becomes important in rabies. The case report showed that group patients have a higher survival rate. A patient who survived post-rabies infection has severe neurologic sequelae. Bats have bitten in America, making them less pathogenic to infect humans.[39]

10. CONCLUSION

Rabies has been known for a long time as a fatal disease. However, it still has a high mortality rate and is a neglected disease. Rabies infection spreading in Indonesia is usually mediated by dog biting. Understanding rabies prevention through vaccination and control of wild animals becomes essential to reducing rabies cases in Indonesia. Anti-rabies vaccines and anti-rabies serum in dog-bitten cases can reduce the progressivity of the disease. Besides that, many symptomatic therapies can be given in rabies cases.

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Conflict of Interest Statement:

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.