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Neuropathogenesis of Human Rabies

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Abstrack
Rabies is an acute infection that occurs in the central nervous system caused by a virus from the Rhabdoviridae family and the Lyssavirus genus that can be transmitted by dogs, cats, monkeys, bats, civets, and wolves. The purpose of writing this literature review is to determine the definition, epidemiology, neuropathogenesis and the role of neurotransmitters, clinical features, diagnosis, and management of rabies. The method used in writing this journal is a literature review, using literature searching. Search the library using website-based search tools, namely Google and Google Scholar using the keywords Rabies, Human Rabies, and Neuropathogenesis of Human Rabies. Free full text English and Indonesian publications. The journals selected in this literature review are 12 journals published between 2015-2021. Rabies infection begins with the transfer of viral microorganisms into the bite wound through the saliva of an infected animal. Rabies virus receptors consist of nicotinic acetylcholine receptors, Neural cell adhesion molecules (NCAM), and Nerve Growth Factor (NGF). Virus replication occurs in skeletal muscle and spreads via motor or sensory nerves to the spinal cord and brain. The virus binds to the nicotinic acetylcholine receptor via the neuromuscular route. There are 3 neurotransmitters that play a role in the neuropathogenesis of rabies, namely acetylcholine, serotonin, and GABA.

Keywords : Rabies; Human Rabies; Neuropathogenesis of Human Rabies.

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Introduction

Rabies is an acute infection that occurs in the central nervous system caused by a virus belonging to the family Rhabdoviridae and the genus Lyssavirus. Animals that can transmit the rabies virus include dogs, cats, monkeys, bats, ferrets, and wolves. Transmission of rabies to humans is generally caused by animal saliva that enters through bites or licks that occur on injured skin or in the eyes, mouth, nose, anus and genitals (Purnamasari and Putra 2017).

Rabies has been found in 150 countries around the world and causes about 55,000 deaths every year. In Indonesia, rabies cases were found in 24 out of 34 provinces and 10 provinces were declared free of rabies, including Bangka Belitung, DKI Jakarta, Riau Islands, Central Java, DI Yogyakarta, East Java, West Papua, West Kalimantan, Papua and NTB (Kemenkes, RI). , 2020). Most cases of rabies occur in children under 15 years of age. In humans, the incubation period of the virus varies widely, from days to years, with an average of 2 to 3 months and is influenced by the location, extent and depth of the wound, and the distance between the wound site and the central nervous system (Salom&#65533;o et al. 2017).

Viruses that successfully enter the human body will replicate in the cytoplasm, move from cell to cell until they reach nerve receptors and enter the nervous system, travel to the central nervous system where the virus will concentrate in the brain and spinal cord (Shimla and Pradesh, 2020). Rabies affects the brain and spinal cord with early symptoms including flu, fever, headache and infection which can quickly progress to hallucinations, paralysis and even death (Yousaf et al. 2012). Vaccination is highly recommended for anyone who has a high risk of exposure to the rabies virus such as laboratory staff, veterinarians, and those who work with wild animals to reduce the risk of infection from rabies (Crowcroft and Thampi 2015).

The purpose of writing this journal is to determine the definition, epidemiology, neuropathogenesis, and the role of neurotransmitters, clinical features, diagnosis, and management of rabies.

Method

The method used in writing this journal is a literature review, using literature searching. Search the library using website-based search tools, namely Google, and Google Scholar using the keywords Rabies, Human Rabies, and Neuropathogenesis of Human Rabies. English and Indonesian publications Free full text. The journals selected in this literature review are 12 journals published between 2015-2021.

Research Result

Definition

Rabies is an acute, progressive and fatal neuroparalytic viral disease in animal species (Shimla and Pradesh, 2020). According to the Indonesian Ministry of Health, Rabies, or commonly referred to as mad dog disease, is an acute infectious disease caused by the rabies virus in the central nervous system (Kemenkes RI, 2016). It is called mad

dog disease because in Indonesia, the most common animal that transmits rabies is dogs (98%). In addition to dogs, animals that transmit the rabies virus include cats, monkeys, bats, civets, and wolves. Rabies is caused by a virus from thefamily Rhabdoviridae and thegenus Lyssavirus (Purnamasari and Putra 2017).

Epidemiology

Rabies infection is spread all over the world, almost on all continents except Antarctica (Purnamasari and Putra 2017). Rabies itself ranks as the 10th cause of death from infectious diseases in the world. It is estimated that 2.5 billion people in 100 countries are at risk of contracting rabies. According to WHO, the highest mortality rate was experienced in India (36%) and the lowest in Cambodia and Magnolia (Shimla and Pradesh, 2020). Approximately 55,000 individuals die annually from rabies and >15 million have received vaccines to prevent the disease from developing. 40% of all victims bitten by animals suspected of rabies are children aged 15 years and under (Kemenkes RI, 2016). Southeast Asia itself is one of the rabies endemic areas (Purnamasari and Putra 2017). Around 45% of rabies deaths come from Southeast Asia (Novita 2019).

Rabies in Indonesia has existed since the 18th century (Novita 2019). The first case was reported in a buffalo by Esser in 1884, followed by Dizziness in 1889 in dogs and Eileris de Zhaan in 1894 in humans, where all cases came from West Java, Cirebon area and then spread to other areas (Kemenkes RI, 2016). Data as of 2017, it is said that rabies has spread in approximately 25 provinces in Indonesia (Novita 2019). In 2014, 42,958 cases of GHPR (bites of animals with rabies) were found, with the most cases being in Bali (21,161 cases), NTT (5,340 cases), and North Sulawesi (3,601 cases) (Purnamasari and Putra 2017).

Neuropathogenesis

Humans can become infected with the rabies virus with the most frequent infection being through the bite of infected dogs, cats, and other wild carnivorous species such as insectivorous bats. Herbivorous animals such as cattle, horses, deer, and other herbivores can become infected with rabies, although they can transmit the virus to other animals and humans this is rare (Shimla and Pradesh, 2020).

The infection can occur initiated by the transfer of viral microorganisms into the bite wound through the saliva of an infected animal. Rabies virus receptors consist ofreceptors nicotinic acetylcholine, Neural cell adhesion molecules (NCAM), and Nerve Growth Factor (NGF). Virus replication occurs in skeletal muscle and spreads via motor or sensory nerves to the spinal cord and brain. The virus binds to the nicotinic acetylcholine receptor via the neuromuscular route. The virus then travels to the Central Nervous System (CNS) along with motor and sensory axons via retrograde fast axonal transport at a speed of 12-100 mm per day (Shimla and Pradesh, 2020).

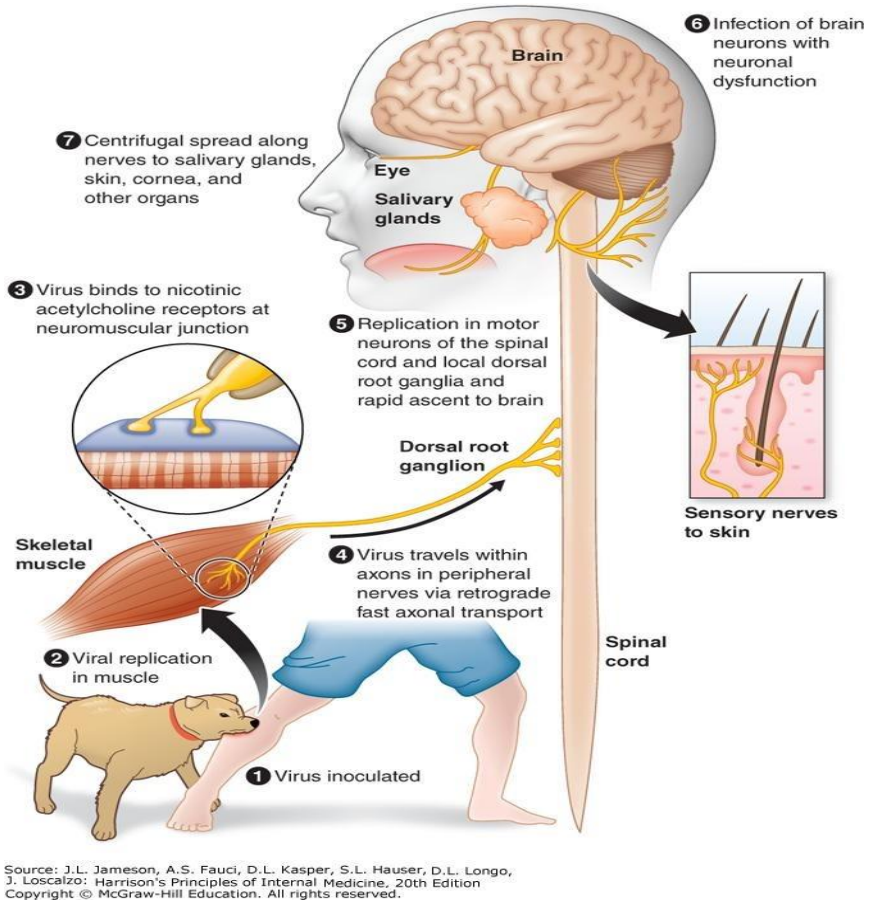
The virus enters the peripheral nervous system through the neuromuscular junction, and travels rapidly centripetally to the central nervous system, especially to the nearest

sensory or motor nerves in the dorsal root ganglion in the spinal cord where the virus replicates (Shimla and Pradesh, 2020).

Once the infection has developed in the spinal cord or brainstem neurons, the rabies virus spreads rapidly throughout the central nervous system by rapid axonal transport along with neuroanatomical connections. Under natural conditions, infection with the rabies virus in the CNS causes only relatively mild neuropathological changes, so that neurological disease in rabies is caused by nerve dysfunction along with nerve cell death (Shimla and Pradesh, 2020).

In the later stages of infection, the virus can be transported centrifugally to many peripheral tissues and organs, such as the respiratory tract, cornea, scalp and neck, adipose tissue, adrenal medulla, and renal parenchyma. Although replication is widespread, not many pathological changes can be observed in the brain except for Negri bodies. Other factors that may contribute to this disease process are abnormalities in neurotransmitters, accumulation of nitric oxide, and proinflammatory cytokines such as Tumor Necrosis factor-alpha (TNF-α) (Shimla and Pradesh, 2020).

Figure 1.



Neuropatogenesis Rabies (Tanzil, 2017).

Role of Neurotransmitters

Rabies virus causes neuronal infection which results in abnormal function of neurotransmitters such as acetylcholine, serotonin, and GABA. These three neurotransmitters are neurotransmitters that affect nerve dysfunction in rabies (Imelda and Sudewi 2015).

Acetylcholine is secreted by neurons mostly located in brain areas (pyramid cells in the motor cortex, some basal ganglia neurons, skeletal muscle innervation motor neurons, preganglionic neurons of the autonomic nervous system, prostaglandin neurons of the parasympathetic nervous system, and some postganglionic neurons of the nervous system sympathetic) and has both excitatory and inhibitory effects on some peripheral parasympathetic nerve endings, such as vagus nerve cardiac inhibition. A study standard challenge virus (CVS) strains of peripheralfrom the brains of rabies-infected rats by looking at binding to the muscarinic acetylcholine receptor hypothesized that decreased cholinergic neurotransmission may be the basis of neuronal dysfunction in rabies. To examine this neurotransmission defect, labeled 3H antagonists were used Quinuclidinyl Benzylate (QNB), where after 120 hours, 10-20 hours after death, the 3H binding of QNB labels to AChRs decreased significantly. The greatest decrease was found in the hippocampus, and slightly in the cortex and caudate nucleus. The hypothesis of the binding of the rabies virus to the acetylcholine receptor in the brain is doubtful because other studies conducted on mice showed that there was no significant difference in mice infected with the CVS strain and in controls. This is indicated by the enzymatic activity of choline acetate transferase and acetylcholine esterase in the cerebral cortex and hippocampus. The binding of QNB to muscarinic acetylcholine receptors in the cerebral cortex or hippocampus was found to be similar between infected and control mice. The differences in species and inoculation pathways (peripheral/intracerebral) between mice and rats may be the reason for the different results in the two studies. The greatest reduction in binding occurred in the hippocampus, and was observed in the cerebral cortex and in the caudate nucleus. In rabies-infected dogs, the specific binding of 3H-QNB is naturally reduced by 35% in the hippocampus and 72% in the brainstem. However, in uninfected control dogs, there was no decrease in other brain areas. These results are the same for paralytic rabies and fierce rabies (Imelda and Sudewi 2015).

The role of serotonin in rabies infection also needs to be considered, this has an important role in the pathogenesis of rabies because neurotransmitter damage will involve other neurotransmitters. Serotonin itself is secreted by the nucleus of the nucleus raphe in the medial brainstem and projects in most areas of the brain, especially to the dorsal root of the spinal cord and the hypothalamus. This neurotransmitter has a wide distribution in the brain and plays a role in memory, pain perception, inhibits pain pathways in the spinal cord, and acts on the higher nervous system to help regulate volition and behavior and play a role in controlling the wake-sleep cycle. Experiments on mice to see changes in sleep stages in rabies have been carried out by studying the chain that binds to the serotonin receptor, namely 5-hydroxytryptamine receptor (5-HT) in CVS strains of rat brain. The results showed that the binding of the 5-HT subtype receptor, namely 5-HT1,

using [3H]5-HT was not affected in the hippocampus. However, after inoculation of the CVS strain into the masseter muscle, there was a sharp decrease in B-max in the cerebral cortex for 5 days. With the introduction of 5-HT1A, 5-HT1B, and 5-HT receptors, the binding of [3H]5-HT to receptors in the cerebral cortex was reduced by 50% for 3 days after inoculation, whereas the specific chain binding for 5-HT1A and 5-HT receptors was reduced. HT1B is not affected. The results of this study indicate that rabies virus infection affects other 5-HT receptors in the cerebral cortex. In rabies studies conducted in squirrels, there were important serotonergic projections from the dorsal raphe nucleus in the brainstem to the cerebral cortex and early infection of the raphe nucleus in the mesencephalon. Reduced serotonin 5-HT receptor binding may be a direct effect of infection of non-cortical areas or part of the physiological response to stress due to infection. From these two studies, it can be concluded that in rabies, serotonin disorders play an important role in nerve dysfunction (Imelda and Sudewi 2015).

GABA causes inhibition and is secreted by nerve endings in the spinal cord, cerebellum, basal ganglia, and most of the cortex. In the central nervous system of rabies-infected mice, a decrease in GABA formation and binding, especially in primary cortical neurons, was found with a decrease of about 45% 3 days after infection which coincided with the time of viral growth. In 98 mice compared with control, there was an increase in GABA binding. However, this abnormality of GABA uptake and release in the pathogenesis of rabies in vivo has not yet been determined (Imelda and Sudewi 2015).

Clinical overview

The rabies virus must travel to the brain after a bite or exposure for it to cause symptoms. The delay between exposure to the onset of symptoms is called the incubation period. The incubation period can last from one week to one year depending on the location of the bite or exposure from the brain, the type of rabies virus, and the immune system (World Health Organization, 2021).

After the incubation period an infected person begins to experience symptoms of rabies, this period is called the acute period. The acute period can last from two to ten days. Early symptoms of rabies are similar to those of the flu, such as weakness, fever, or headache that lasts a few days. If exposed to animal teeth, the bite site will feel painful, such as prickling, tingling, or a burning sensation (World Health Organization, 2021). Based on the weight of the symptoms, rabies grouped into two namely:

- Rabies is malignant symptoms in the form of hyperactivity, excitement, hydrophobia (fear of water), sometimes aerophobia (fear of fresh air). Death can occur within a few days due to cardiac arrest (World Health Organization, 2021).
- Paralytic rabies accounts for 20% of all cases of rabies in humans. Symptoms are milder and last longer. Symptoms include muscle paralysis that occurs slowly starting from the site of the bite, then the infected person slowly goes into a coma and eventually death (World Health Organization, 2021).

Diagnosis

Rapid, sensitive, specific, and economical laboratory tests are needed to provide timely prophylaxis so that the patient is protected from unnecessary physical and psychological trauma and the patient is spared the financial burden if the animal is not infected with rabies. In addition, laboratory identification helps determine disease epidemiology patterns and helps develop rabies control programs (WHO et al. 2019).

The method for diagnosing rabies, which has become the gold standard in animals, uses the direct fluorescent antibody (DFA) test because it has high sensitivity and specificity, thus providing accurate clinical information about the status of rabies in animals for the purpose of treating people who are exposed to it. Several tests that can be used to establish a diagnosis other than DFA include direct rapid immunohistochemistry test (DRIT), rapid immunochromatographic test (RIDT), rabies tissue culture infection test (RTCIT), and mouse inoculation test (MIT) (WHO et al. 2019).

Management

1. Wound Handling and Provision of Antiseptic

Wounds due to bites/licks are immediately washed with soap and running water for at least 15 minutes, and followed by the provision of antiseptics such as povidone-iodine, 70% alcohol, and other antiseptic substances. Exposure Categories and Treatment Recommendations according to WHO based on the following table:

Table 1.

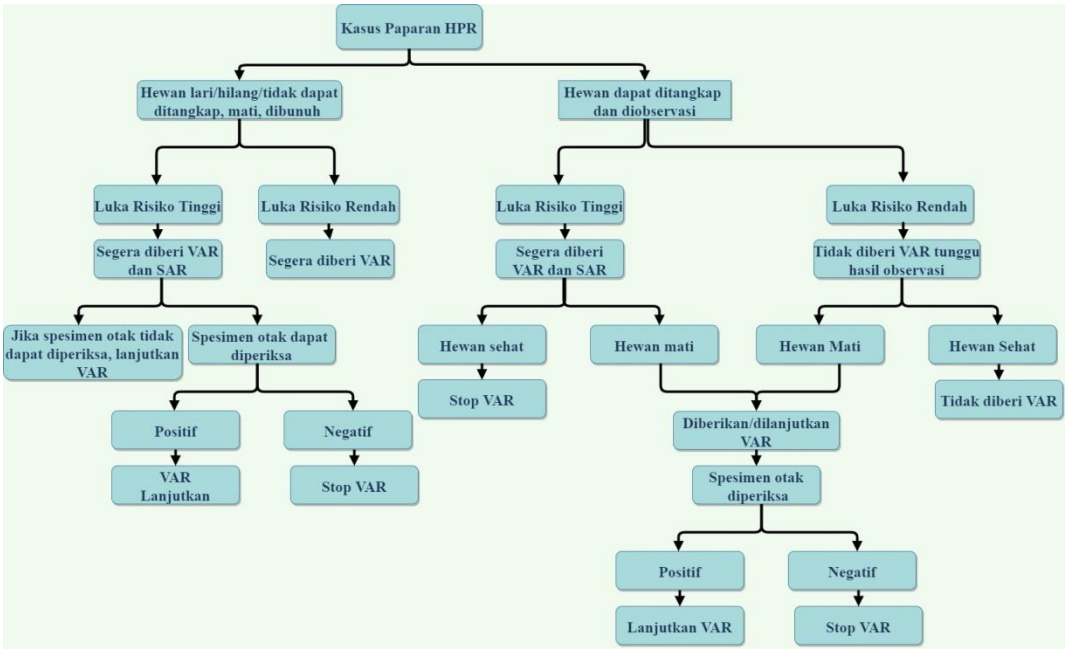
Category	Type of contact (with suspect pets or confirmed rabies, wild animals, or animals that cannot be observed)	treatment recommendations
I	- Touching or feeding animals - Lick on intact skin	- Perform wound washing - Not given vaccine or serum
II	- Biting open skin - Minor scrapes or abrasions without bleeding	- Perform wound washing and wound care - Immediately given anti-rabies vaccine. Stop giving the vaccine if the results of observation for 10 days are healthy animals or if the results of laboratory tests on animals are negative with adequate examination techniques
III	- Bites or scrapes causing single or multiple transdermal sores, licking of broken skin - Contamination of mucous membranes with saliva from animal licks - Exposure to bats	- Perform wound washing with wound care - Vaccination is immediately given if the results of observation for 10 days are healthy animals or if the results of laboratory examinations on animals are negative with adequate examination techniques.

Exposure Categories and Recommended Procedures (Kemenkes RI., 2016).

2. Administration of Anti-Rabies Vaccine (VAR) and Anti Rabies Serum (SAR)

The purpose of administering VAR is to awaken the immune system in the body against the rabies virus and it is hoped that the antibodies formed will neutralize the rabies virus. However, if the rabies virus has reached the central nervous system, giving this anti-rabies vaccine will no longer provide any benefit. Therefore, VAR administration should be carried out as soon as possible. The provision of VAR and SAR needs to be considered based on other conditions as in the flowchart below:

Figure 2.



Provision of VAR and SAR (Purnamasari and Putra 2017).

Anti Rabies Vaccine (VAR)

1. Post Exposure Prophylaxis (PEP)
   a. Purified Vera Rabies Vaccine/PVRV (Verorab)

Table 2.

Doses		way of giving	Time of giving
Child	Adult		
0,5 ml	0,5 ml	IM	• Day 0 → doses (right and left upper arm or right and left thigh for children <1 year) • Day 7 → 1 doses • Day 21 → 1 doses

PEP Verorab (Kemenkes RI., 2016).

b. Purifed Chick Embriyo cell-culture Vaccine/PCECV (Rabipur)

Table 3.

Doses	Way of giving	Time of giving
1 ml	IM	• Day 0 → 2 doses (right and left upper arm or right and left thigh for children <1 year old) • Day 7 → 1 doses • Day 21 → 1 doses

PEP Rabipur (Kemenkes RI., 2016).

2. Pre Exposure Prophylaxis (PrEP)

a. Purified Vera Rabies Vaccine/PVRV (Verorab)

Table 4.

Doses	Way of Giving	Time of giving
0,5 ml	IM of upper arm	• Day 0 → 1 doses • Day 7 → 1 doses • Day 21 or 28 → 1 doses

PrEP Verorab (Kemenkes RI., 2016).

b. Purifed Chick Embriyo cell-culture Vaccine/PCECV (Rabipur)

Table 5.

Doses	Way of giving	Time of giving
1 ml	IM	• Day 0 → 1 doses • Day 7 → 1 doses • Day 21 or 28 → 1 doses

PrEP Rabipur (Kemenkes RI., 2016).

Serum Anti-rabies (SAR)

1. Serum Homolog (Humam Rabies Immunoglobulin/HRIG)

Table 6.

Doses		Way of giving	Time of giving
Child	Adult		
20 IU/ Kg BB	20 IU/ Kg BB	Infiltrate around the wound as much as possible, the rest is injected intramuscularlyr	Together with day 0 VAR administration

Serum Homolog (Kemenkes RI., 2016).

2. Serum Heterolog

Table 7.

Doses		Way of giving	Time of giving
Child	Adult		
40 IU/Kg BB	40 IU/Kg BB	Infiltrate around the wound as much as possible, the remainder is injected IM in the gluteal region	Simultaneously with day 0 VAR administration

Serum Heterolog (Kemenkes RI., 2016).

Conclusion

Rabies is an acute infectious disease caused by the rabies virus in the central nervous system, which belongs to the family Rhabdoviridae and genus Lyssavirus. Rabies infection spreads almost all over the world with a mortality rate of about 55,000 people per year with 45% of deaths from Southeast Asia as a rabies endemic area. In Indonesia, rabies was first discovered in West Java and spread to other areas to infect around 25 provinces per the year 2017. Humans are infected with rabies generally through the bite of animals such as dogs, cats, and other infected animals and other carnivorous species such as bats.

Early symptoms of rabies are similar to those of the flu, such as weakness, fever, or headache that lasts a few days. If exposed from animal teeth, at the site of the bite will feel pain, such as prickling, tingling, or burning sensation. Symptoms of rabies are divided into malignant and paralytic rabies symptoms. The method for diagnosing rabies, which has become the gold standard in animals, uses the direct fluorescent antibody (DFA) test, and other examinations in the form of direct rapid immunohistochemistry test (DRIT), rapid immunochromatographic test (RIDT), rabies tissue culture infection test (RTCIT), and mouse inoculation test. (MIT). Handling for rabies patients can be done by handling wounds and administering antiseptics as well as administering the anti-rabies vaccine (VAR) and anti-rabies serum (SAR) to avoid transmission.

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