Rabies- A Zoonotic Disease

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ABSTRACT

Rabies, one of the earliest recognized viral diseases, causes encephalitis in humans and other mammals. It is the biggest public health risk that firstly appeared about 4,000 years ago and is considered one of the deadliest diseases with 100% death rate in the twenty-first century. It is a zoonotic and neglected disease that causes around 60,000 human fatalities annually throughout the world. More than 99% of cases of rabies in humans involve dogs. Rabies lyssa virus belongs to the family Rhabdoviridae. After infection takes place within the neuronal cell the virus starts using host machinery, as it reaches cells of the spinal cord, brain stem, and sensory ganglia where replication occurs. Incubation periods vary greatly among different species from days to years. After the incubation period, prodome stage appears characterized by pain, numbness, and itching at the site of the bite, pyrexia, fatigue, and headache. Changes in behavior become apparent like anxiety, agitation, insomnia, and depression. The prodromal phase is followed by the neurological phase which causes hallucinations, disorientation, paralysis, hydrophobia, hyperventilation, hypersalivation, and seizures followed by coma and death. An antemortem diagnosis is done by detection of rabies antigen and with serological testing. Once the clinical signs of rabies become obvious it is difficult to cure the disease and becomes fatal for both animals and human. However, rabies can be prevented by wound cleaning and administration of pre and post exposure vaccine.

Keywords: Rabies virus, encephalitis, lyssavirus, rabies prevention, virus transmission, rabies vaccine.

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1. INTRODUCTION

Rabies, one of the earliest recognized viral diseases, causes encephalitis in humans and other mammals (Scholand et al. 2011). It first appeared about 4,000 years ago and is considered one of the deadliest diseases with 100% death rate. It is the biggest public health risk in the twenty-first century except for Antarctica. Each year, thousands of deaths are documented, with the majority of cases being reported in Asia and Africa. Dog bites are the primary cause of nearly in all human instances of rabies. Neurotropic viruses of the genus Lyssa virus are responsible for its onset. Although zoonotic but it is a neglected disease in humans and animals. Children between 5 and 14 years are frequent victims (Rivera et al. 2018). Children under the age of 15years frequently die of dog bites in Africa and Asia. According to preliminary data, rabies causes around 60,000 human fatalities annually throughout the world. With such a big number, it can be inferred that rabies causes a yearly economic loss of over 4 billion dollars and leads to the loss of over 2 million disability-adjusted life years (DALYs). More than 99% of cases of rabies in humans involve dogs. Therefore, preventing dogs, especially stray dogs, from roaming freely can help stop the spread of rabies. In America, rabies has been successfully eradicated in both dogs and terrestrial species, while in Western Europe; rabies has been successfully controlled in canine populations (Banyard et al. 2014).

1.1. EPIDEMIOLOGY OF RABIES

Rabies is present all over the world except Antarctica. Over 95% of human deaths occur in Asia and Africa. Annually approximately 60000 deaths occur worldwide. In 2015, India (approximately 20,847) followed by China (approximately 6000) and the Democratic Republic of Congo (approximately5600) had the most cases (Coudeville et al. 2015).

1.2. RABIES IN PAKISTAN

Rabies is one of the leading animal-transmitted diseases in the sub-continent. In Pakistan alone, rabies contributes to about 2000 to 5000 deaths in a year (Mughal and Ali 2018). Unfortunately, only one method is applied for prevention which is killing stray dogs and an immunization program for the victims (Khan et al. 1976). Due to failure in controlling rabies, it remains endemic in Pakistan (Nawaz et al. 2022). Factors like in-adequate medical training, lack of awareness, and shortage of availability of vaccines contribute to a high mortality rate (Mubashir and Hussain 2021).

1.3. RABIES IN INDIA

India has the greatest rate of human rabies in the world. The number of cases increased since 2001, because of high stray dog's population. An estimated 20,000 people die every year from rabies in India, more than a third of the global total (Dyer et al. 2012).

1.4. RABIES IN AUSTRALIA

Australia is officially declared as rabies-free zone. However, the Australia Bat Lyssa Virus (ABLV) was discovered in 1996 (Makita et al. 2019).

1.5. RABIES IN UNITED STATES

Canine rabies was eradicated from the US but it is still present in wild animals. From 1960 to 2018, about 125 human rabies cases were reported in the United States out of which about 36 (28%) cases were

Fig. 1: Children playing with stray dog. A picture captured in a village in Pakistan.

because of dog bites during international travel. Among 89 infections present in the US, 62 (70%) are reported to be because of bats. In 2021, only one case of human rabies was recorded in the US in nearly 3 years (Pearson et al. 2019).

1.6. RABIES IN EUROPE

Very few cases of rabies are reported annually in Europe.

1.7. RABIES IN UNITED KINGDOM

The United Kingdom was declared free of rabies in the early 20th century except for rabies-like European bat 2 lyssavirus (EBLV-2) in a few Daubenton's bats (Easmon 2003). In 1902, last death from indigenous rabies was reported from UK (McIntyre et al. 2003). Since 2000, there have been4 deaths reported due to rabies that were transmitted due to dog bites in international travels.

1.8. RABIES IN SWEDEN AND NORWAY

Sweden and Norway were declared free from rabies in 1886. Rabies antibodies were found in bats but no virus was found (Tryland et al. 2022).

1.9. RABIES IN MEXICO

Mexico was certified by WHO as being dog-transmitted free rabies in 2019 because no case of dog-human transmission was recorded in 2 years.

2. ETIOLOGY OF RABIES

Rabies virus belongs to the family Rhabdoviridae, and order Mononegavirales. It is a negative-stranded RNA virus having bullet shape. It consists of three genera of animal viruses including, Lyssa virus, Ephemer virus, and Vesiculo virus. Genus Lyssa virus includes Rabies virus, Mokola virus, Duvenhage virus, European bat virus 1 & 2, and Australian Bat virus. The RNA genome of Lyssa viruses is 12 kilo bases long and not divided into segments. It is of negative polarity, encoding 5 viral proteins (3' to 5') including nucleoprotein N, phosphor protein P, matrix protein M, glycoprotein G, and polymerase L. Its size ranges from 100-300nm long and 75nm in diameter (Hyatt et al. 1998).It is composed of two functional and structural units:
The outer envelope is made up of a lipid bilayer. Spike-like projections corresponding to G-Protein trimmers are present on it. These spikes recognize and bind cell receptors. While G-protein is important for Lyssavirus pathogenicity and also for induction of immune response (Juozapaitis et al. 2007).
The internal ribonucleocapsid (RNP) is made up of genomic RNA associated with protein N, polymerase L, and its cofactor protein P. This internal structure ensures genomic transcription and replication in the cytoplasm. Ribonucleocapsid is of helical structure (Granzow et al. 2010).
The matrix protein M is present in the middle of ribonucleocapsid and envelope. It is responsible for the bullet-shaped morphology of the virus and its budding (Granzow et al. 2010).

3. PATHOGENESIS AND CLINICAL PRESENTATION OF RABIES

3.1. PATHOGENESIS

The virus is excreted in the saliva of an infected animal and deposited through the skin into subcutaneous tissue and muscles of the host (Suja et al. 2016). After entry, the virus binds to the cell receptors. It replicates within striated muscles or connected tissue at the site of inoculation and then enter peripheral nerves by a neuro-muscular junction (Chakrabharti 2007). After infection takes place within the neuronal cell the virus starts using host machinery, as it reaches cells of the spinal cord, brain stem, and sensory ganglia where replication occurs (Fooks, Banyard et al. 2014). Then the virus travels by fast axonal from the spinal cord to the brain, and up to this stage, no clinical sign appears as insufficient viral antigens are present to trigger an immune response of the body. After reaching central nervous system (CNS), the virus replicates extensively and, in this stage, clinical signs appear and it can become fatal for the animal (Banyard et al. 2014). Extensive infection spreads in the brain and leads to virus dissemination by neurons into different body sites. Rabies virus now reaches peripheral sites and eventually reaches non-nervous tissue like taste buds, olfactory cells, thymus, salivary glands, and pass in to oral and nasal secretions (Chakrabharti 2007). The salivary glands are innervated by the parasympathetic nervous system by submandibular ganglion and glossopharyngeal nerves, sympathetic innervation by the superior cervical ganglion, and by the afferent innervations (Banyard et al. 2014). On invading the brain, virus damages the brain stem and medulla causing nerves to undergo degeneration. Ultimately, paralysis of various muscles and clinical signs become visible (Chakrabharti 2007).
Atthe microscopic level, neural degeneration and perivascular infiltration occur. Formation of Negri Bodies is the characteristic feature for the identification of rabies (Chakrabharti 2007). They are granulated structures observed on the site of replication.

4. INCUBATION PERIOD

Incubation periods vary greatly among different species. Generally, it ranges from 1-3 months in dogs. In some cases, it is also extending up to years. In human sit mostly lasts for 3-8 weeks, and sometimes more than 6 months (Iowa 2015). Incubation period variation depends upon factors including the age of the animal, virulence of the virus, virus concentration, severity of bite, and distance of bite from CNS (Chakrabharti 2007). The nearer the bite is from the CNS more rapidly infection develops and clinical signs appear (Baron 1996). It also depends upon the species of animal. The virus hides in safe sanctuaries in the host during prolonged incubation periods (Suja et al. 2016).

5. CLINICAL STAGES AND SYMPTOMS OF RABIES

5.1. RABIES IN HUMAN

Five stages of rabies are found in humans, incubation, prodrome, acute neurologic period, coma, and eventually death (Baron 1996). After the incubation period, prodome stage appears characterized by pain, numbness, and itching at the site of the bite, and nonspecific clinical signs are likely to appear including pyrexia, fatigue, and headache. Changes in behavior become apparent like anxiety, agitation, insomnia, and depression. The prodromal phase is followed by the neurological phase which causes hallucinations, disorientation, paralysis, hydrophobia, hyperventilation, hypersalivation, and seizures followed by coma and death (Iowa 2015).

5.2. RABIES IN DOG

In animals, rabies is mostly differentiated into two forms based on signs and symptoms; furious (encephalitic) and dumb (paralytic) rabies. Another type, atypical rabies, is also observed.

5.2.1. FURIOUS RABIES

It is characterized by aggressive or excited behavior. In this condition dogs tends to bite inanimate and animate objects, does not obey their master, have violent and frenzy behavior, tend to bite inedible things (like stone, and wires), bite other animals and humans, unusually stay alert, tend to bite imaginary objects, drooling of saliva, pupil dilation, lacrimation, hydrophobia, hallucinations, aerophobia. Paralysis of pharyngeal and laryngeal muscles leads to the paralysis of throat muscles hence dog may be unable to swallow food and drink water (Chakrabharti 2007).
As the condition becomes severe, dog becomes more aggressive, photophobia occurs, excessive sweating, protrusion of tongue, characteristic change in the bark, dyspnea, ascending paralysis and coma. This condition may last for as long as 10 days, and eventually death occur (Chakrabharti 2007).

5.2.2. DUMB RABIES

Paresthesia and weakness are characteristic of the onset of the disease (Suja et al. 2016). In this form there is paralysis of the lower jaw, tongue, larynx, and hindquarters, the dog can’t bite but the saliva is still infected. Dogs are unable to bark due to the paralysis of throat muscles. Dog produce voices like howling. Moreover, dogs can’t close their mouths because of the hanging of lower jaw. Excessive gagging may also be observed (Chakrabharti 2007).In the terminal stages, the dog shows progressive weakness and paralysis

and ultimately proceeds to coma and death This form lasts for up to 1-7 days. To more or less extent, rabies virus also affects other animals like cats, horses, cattle, sheep, goats, and pigs (Chakrabharti 2007).

5.2.3. ATYPICAL RABIES

This type is mostly associated with bat bites. It may have symptoms of both furious and dumb rabies. These variations make it very difficult to recognize rabies disease (Rod Brouhard 2021).

6. DIAGNOSIS OF RABIES

Even if a patient may exhibit symptoms that are highly typical for rabies, such as behavioural changes or trouble swallowing clinical observation and examination cannot confirm the diagnosis and can only raise suspicion of rabies. The only way to make a conclusive diagnosis of rabies is to find the virus or some of its particular components using the recommended standard laboratory tests from the WHO and OIE WHO (2013).
In both humans and animals, brain tissue is the ideal specimen for post-mortem diagnosis. The only way to reliably identify an infection in a patient who is suspected of having the disease is intra-vital testing of rabies in animals, that even though it is generally discouraged. The foundation of intra-vital diagnostics in suspect human patients is virus or viral RNA detection (CDC 2011).

7. FINDING THE RABIES ANTIGEN

The fluorescent antibody test (FAT) is most widely used primary diagnostic test for rabies diagnosis in humans and animals. This test is based on antigen detection and regarded as the gold standard for diagnosing rabies by the WHO and OIE. An impression smear formed from a composite sample of brain tissue is treated with anti-rabies serum or globulin that has been fluorescently labelled with fluorescein isothio cyanate (FITC). The fluorescence of certain clumps of rabies virus antigen can be used to identify them under a reflected light (incidental light) fluorescence microscope. The precision, sensitivity, and speed of the FAT allow for results to be routinely obtained within 1 to 2 hours of receiving the specimen. A direct rapid immune histochemistry test (dRIT) is an alternative to fluorescence microscopy (Mani and Madhusudana 2013).

7.1. DIRECT MICROSCOPY: HISTOLOGICAL IDENTIFICATION OF CHARACTERISTIC CELL LESIONS

Histological studies (Seller's Technique) on smears taken from different regions of the brain show aggregation of virus particles called "Negri bodies" which are intra-cytoplasmic inclusion bodies specific to rabies infected neuronal cells. Negri bodies range in size from 3 30mm in diameter. These bodies are often circular or oval, and are profoundly eosinophilic with distinctive basophilic granules that are frequently grouped in the shape of a rosette inside the eosinophilic matrix (Ravisse et al. 2017).
Seller's method on unfixed tissue smears is a straightforward, quick test, but it only works on fresh samples and has a relatively poor sensitivity. Staining methods for paraffin-embedded sections of brain tissue take longer, are more expensive, and are less accurate. Histological techniques are much less sensitive than immunological methods, especially in the case of autolyzed specimens, and are no longer recommended for primary diagnosis, both in humans and animals (Ponfa et al. 2016).

7.2. CLINICAL EVALUATION

When evaluating a suspected case of rabies, healthcare professionals typically consider the following clinical factors:

7.3. CLINICAL SIGNS AND SYMPTOMS

7.3.1. EXPOSURE HISTORY

To assess the risk of rabies transmission, a detailed study of the patient's history is necessary. The main topics of discussion should be possible animal contact, especially bites and scratches, as well as any trips to areas where rabies is an endemic disease.

7.3.2. INCUBATION PERIOD

The rabies incubation period can last anywhere from a few days to several years. The amount of time that has passed since the patient may have been exposed to the virus is crucial since it can assist in predicting the possibility of rabies infection (Sajjad et al. 2017).

7.3.3. DIAGNOSTIC TESTS

Typically, laboratory testing is necessary for a rabies diagnosis. The direct fluorescent antibody (DFA) test is used to find the rabies virus in skin biopsy samples taken from the nape of the neck. Additionally, viral RNA can be found in saliva, cerebrospinal fluid, or tissue samples using the reverse transcription-polymerase chain reaction (RT-PCR) (CDC 2011).

7.3.4. PROGNOSIS

Once rabies clinical symptoms appear, the condition is nearly invariably fatal. Since there are so few confirmed cases of survival, prompt post-exposure prophylactic delivery and early diagnosis are crucial (Nadeem and Panda 2020).

7.3.5. POST-EXPOSURE PROPHYLAXIS (PEP)

PEP entails meticulous wound cleaning, rabies vaccination, and injection of rabies immunoglobulin (RIG) for those who have experienced high-risk exposures. To increase the possibility that rabies symptoms won't manifest, PEP should be started as soon as possible.

8. LABORATORY TECHNIQUES FOR RABIES DIAGNOSIS

Laboratory methods that can identify the presence of the virus or its antibodies in the body are frequently used to diagnose rabies. Here are a few typical methods used in laboratories to identify rabies (Rao 2019).

8.1. DIRECT FLUORESCENT ANTIBODY (DFA) TEST

The most popular and trustworthy laboratory test for rabies diagnosis is DFA. It involves using fluorescent dyes that precisely bind to the rabies virus antigens to stain samples of brain tissue from the suspected animal or human. The diagnosis is supported by the discovery of fluorescently labelled viral particles (Fooks et al. 2018).

8.2. POLYMERASE CHAIN REACTION (PCR)

The PCR method is used to detect and amplify the genetic material (RNA) of the rabies virus. It is a very sensitive technique that can find very small amounts of the virus. PCR is frequently applied to samples of cerebrospinal fluid, saliva, or brain tissue (Isloor et al. 2018).

8.3. SEROLOGY

These tests are frequently used to verify prior virus exposure or to evaluate the efficacy of rabies immunization. The IFA is most popular serological test for rabies WHO (2013). Other test is ELIZA and RFFIT (Rapid Fluorescent Focus Inhibition Test).

8.4. VIRUS ISOLATION

In this method, the rabies virus is grown in laboratory animals (such as mice or cell cultures) by injecting brain tissue samples or other body fluids into the animals. Virus isolation is less frequently employed than other diagnostic techniques because it takes time and sophisticated equipment (Huang et al. 2018).

8.5. HISTOPATHOLOGY

Brain tissue samples from probable rabies patients can reveal distinctive changes through histopathological analysis, including inflammation and the presence of inclusion bodies (Negri bodies). This method is often used in conjunction with other laboratory tests because it cannot reliably confirm a diagnosis on its own.

9. IMMUNOHISTOCHEMISTRY (IHC)

The rabies virus antigen can be found in formalin-fixed tissues using IHC procedures, which are sensitive and specific. Before being embedded in paraffin and sectioned onto formalin-fixed paraffin-embedded slides, tissues treated in formalin must first be processed using standard histologic techniques. Specifically designed anti-rabies monoclonal or polyclonal antibodies are used to identify the rabies viral antigen. Compared to histologic staining techniques like hematoxylin and eosin (H&E) and Sellers stains, IHC testing is more sensitive and precise (Alizadeh et al. 2019). Fig. 2 and 3 shows the positive and negative results for the presence of virus inside the brain neural cells.

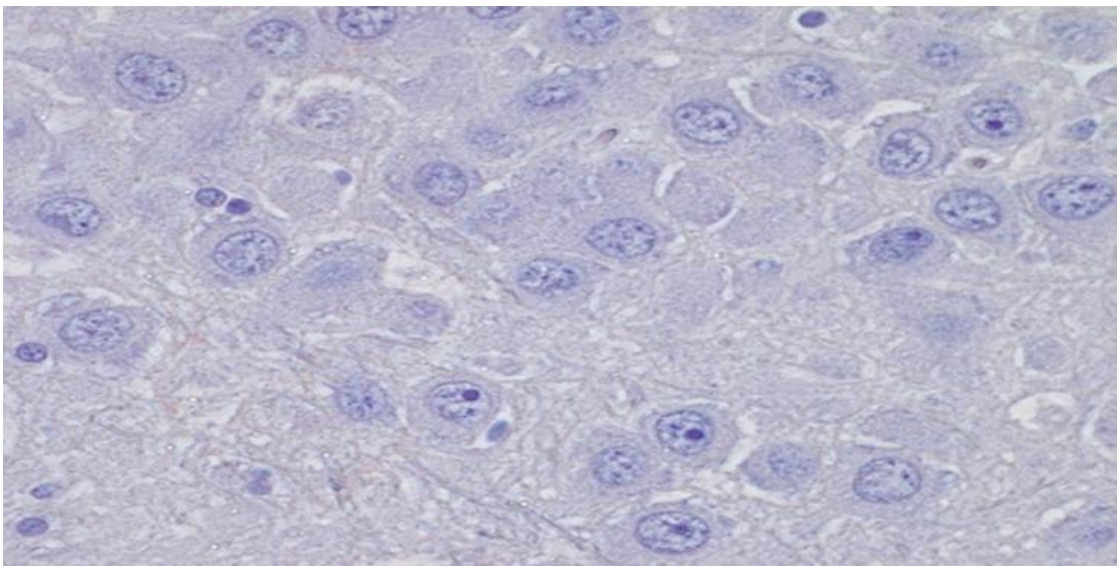

Fig. 2: Brain neural cells with intracytoplasmic inclusions that have been infected with rabies. Using the Streptavidin-biotin complex staining technique, the red stain denotes the presence of rabies viral antigen.

10. SEROLOGICAL TEST

There isn't currently a widely used serological test for identifying human rabies. The direct fluorescent antibody (DFA) test, which includes evaluating brain tissue samples for the presence of the rabies virus, is the only procedure that can be relied upon to accurately diagnose rabies. Usually, this test is carried out after death. The most frequent way to identify rabies in live animals is by looking for certain clinical signs and symptoms and a history of possible virus exposure. The signs and symptoms of rabies can resemble those of other neurological disorders, but they are not unique to rabies. The use of serological techniques, such as enzyme-linked immunoassays (ELISAs), to find rabies antibodies in blood is possible, although these tests are not thought to be diagnostic for an ongoing rabies infection (Singh et al. 2017).

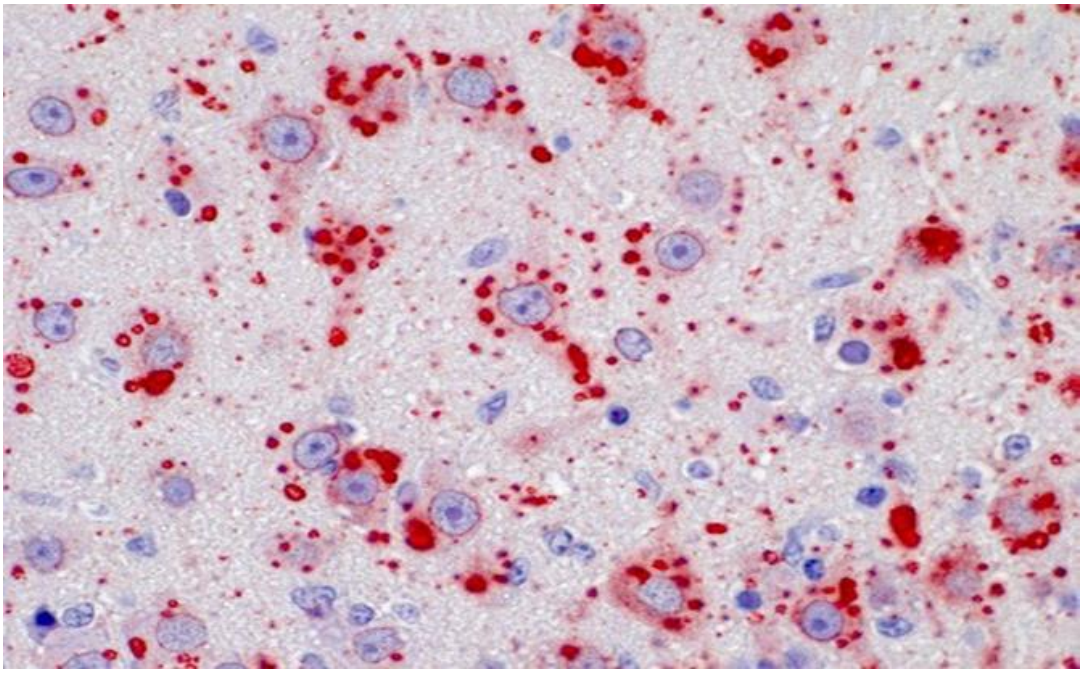

Fig. 3: A result of negative IHC. IHC examination of brain tissue revealed no rabies viral antigen, indicating that no rabies virus was present.

11. DIFFERENTIAL DIAGNOSIS

Here are some conditions that may be considered in the differential diagnosis of rabies.

11.1. OTHER VIRAL ENCEPHALITIDES

Symptoms of rabies can also be caused by illnesses like herpes simplex encephalitis, West Nile virus encephalitis, and Japanese encephalitis. Additionally, these disorders may show neurological signs, a fever, and a change in mental status (Warrell et al. 2017).

11.2. BACTERIAL MENINGITIS

Symptoms of bacterial infections, such as meningococcal meningitis or pneumococcal meningitis, which include fever, headache, stiff neck, and altered mental status, can resemble those of rabies. However, the onset of these illnesses is frequently more abrupt, and they may be accompanied by other infection-related symptoms (Harris and Wittler 2017).

11.3. TETANUS

Tetanus is a bacterial infection brought on by the toxin-producing bacteria *Clostridium tetani*, often known as lockjaw. Muscle spasms, breathing issues, difficulties swallowing, and rigidity of the muscles are possible symptoms. Tetanus and rabies are distinct diseases, yet they could exhibit some of the same neurological signs (Sykes and Creedon 2021).

11.4. GUILLAIN-BARRÉ SYNDROME (GBS)

A rare form of inflammatory disease called GBS damages the peripheral nerves. In severe situations, it might result in paralysis, numbness, tingling, and muscle weakness. Due to neurological symptoms, GBS can occasionally be confused for rabies, however, there are usually no signs of violent behaviour or hydrophobia (Göktepe et al. 2016).

11.5. ACUTE INTERMITTENT PORPHYRIA

The accumulation of porphyrins in the body characterizes this uncommon hereditary condition. Abdominal pain, neuropsychiatric abnormalities, and autonomic dysfunction are possible symptoms. Seizures and neurological symptoms that match those of rabies can occur in severe cases (Lau 2019).

12. TRANSMISSION

There are various routes of transmission of zoonotic agents. Some are transmitted through skin contact without any breakage in the skin's integrity i.e., sarcoptic mange. In case of some diseases breakage in the skin's integrity is essential for transmission like rabies (Acha 1987). A study conducted in the USA in 2009 showed that there were 6690 cases of rabies reported. Wildlife accounts for 93% of the reported cases while that of the domestic animals was7% (Palmer et al. 2011). The saliva of mammals may also contain the rabies virus which may be transmitted through the bite of a rabid mammal. Many cases of rabies from the bites of domesticated animals i.e., cats or rabid cattle had been reported. Various studies from Asia suggest dog bites as the common cause of rabies (Baer et al. 1963; Geneva 2005).
The host species of rabies virus are canine, livestock species, mongoose-associated rabies, felines, raccoon, skunks, vampire bats, and Coyotes(Lima 2013).
About 90% of the infections result from the bite of domesticated animals like dogs and cats due to their close association with human beings. Scratches on the skin infected with saliva have a 50% less risk of infection (Laothamatas et al. 2002; Rupprecht et al. 2008). Mucous membrane exposure and oral routes are ineffective (Abelseth et al. 1971). Intranasal exposure to aerosol droplets is quite dangerous because the olfactory nerve spreads directly to the brain, but natural transmission through this route rarely occurs (Fashinell et al. 1973; Phillpotts et al. 2006). Aerosol inhalation of the rabies virus was observed in a laboratory worker working on the production of a vaccine from brains of rabid sheep and in people inhabited in caves by infected bats (Gibbons 2002).

- Human-to-human rabies transmission is rare but some cases are reported i.e. Donor tissues infected with rabies used for transplantation, similar is the case of recipients of corneal graft (Burton et al. 1979; Fayaz et al. 1996; Wilde et al. 2007; Frisch et al. 2011).
- In some other cases related to the organ transplant from the donor died of rabies (Burton et al. 2005; Schwarting et al. 2010).
- No transfer of infection was recorded from the bite inflicted by rabies-infected humans. Contact of healthcare workers with urine, blood, feces, and non-infectious fluid doesn't cause exposure to disease.

Transmission of virus from mother to breastfed infant has been reported due to the viral secretions in breast milk (Dutta 1998).

- No transplacental transmission has been reported either naturally as well as experimentally in mammals, bats, and dogs (Allen et al. 1963; Montes et al. 1973; Howard 1981).
- Some cases of human rabies during pregnancy have been reported but infants survive through PEP and in some cases without any PEP (Leitritz et al. 1977; Lumbiganon and Wasi 1990; Dacheux et al. 2008).
- There is a risk of transmission of rabies from bats to terrestrial animals.
- Rabies can be transmitted to rabies-free zones and far-off places by the transportation of rabid dogs or other mammals to that area (Wilde et al. 2004; Clifton 2010).

12.1. TREATMENT

Once the clinical signs of rabies become obvious showing that the virus has affected the nervous system, then it is difficult to cure the disease and becomes fatal for both animals and human (Acha 1987).Rabies is a viral disease so no such treatment protocol has been discovered so far to treat this disease but through prevention and control strategies this disease can be prevented (Control and Prevention 2004).

12.2. PREVENTION

Yet the individual affected by the bite of a rabid animal can be prevented from catching the disease, through prophylactic measures taken before the virus could reach the nervous system WHO (2011). WHO stresses on instant and thorough washing of wounds with soap and clean water. After washing apply disinfectants as this reduces the viral load and removes saliva from the wound (Baer et al. 1963).
World Rabies Day was first organized in 2007 by CDC and Alliance for Rabies Control in collaboration with WHO, PAHO, and OIE. This is an important initiative for rabies-affected countries. This includes awareness campaign about rabies through print media and electronic media, seminars and workshops in educational institutes, walks, rallies, different competitions, and free vaccination camps for dogs (Costa 2009).Now it is celebrated every year to create awareness about rabies and preventive strategies to combat rabies.

12.3. CONTROL

Rabies in dogs has been controlled successfully throughout the America while in Western Europe it has been eliminated from dogs and wildlife. Dogs are the main cause of human rabies and accounts for 99% of rabies cases in humans. Therefore, our priority must be to control rabies in the dogs, especially in stray dogs. In this way, we can reduce human rabies cases (Reece and Chawla 2006; Wandeler et al. 2010; Meslin and Briggs 2013).

12.4. VACCINATION PROGRAM

Early neuron tissue vaccine was poorly immunogenic and was made from neuronal tissues of animals. Several doses of vaccine are administered to induce sufficient immunity. Later on in 1940s, these vaccines were replaced by highly immunogenic and safer CCVs (cell culture-derived vaccines) (Warrell 2012).
Pre-exposure prophylaxis (PrEP) is important for individuals travelling to endemic countries. After PrEP, a booster dose is necessary to keep antibody titer high. Booster doses should be administered following the guidelines from the manufacturers (Gautret and Parola 2012).

PrEP vaccine three doses are given through the intramuscular route or intradermal route on following day 0, 7, and 21 (Keates 2010). Table 1 shows the post exposure rabies vaccination regimens recommended by the WHO and the advisory committee on immunization practices by Regimen.

Table 1: The post exposure rabies vaccination regimens recommended by the WHO and the advisory committee on immunization practices by Regimen**.**

	No. of Vaccine Doses	Administration Route	Schedule of Injection
Pre-Exposure Prophylaxis			
Routine intramuscular	3	Intramuscular	At Days 0, 7,21or 28 (single doses)
Routine intradermal	3	Intradermal	At Days 0, 7, 21, or 28 (single doses)
Post Exposure Prophylaxis			
Essen	5	Intramuscular	At Days 0, 3, 7, 14, 28 (single doses)
Zagreb	4	Intramuscular	At Days 0 (double doses), 7, 21 (single dose)
Reduced Four doses	4	Intramuscular	At Days 0, 3, 7, 14 (single dose)
Modified Thai Red Cross	8	Intradermal	At Days 0, 3, 7, 28 (two doses)
Post-exposure Prophylaxis for Vaccinated People			
Two-dose intramuscular	2	Intramuscular	At Days 0, 3 (single dose)
Four-dose intradermal	4	Intradermal	At Day 0 (four doses)

13. PRE-EXPOSURE PROPHYLAXIS

PrEP is a feasible strategy in combating rabies, especially in cases resulting from disguised or unseen exposures and in cases of delayed PEP. The dog bite patients who have been previously immunized through PrEP don't need RIG. PrEP is highly recommended by the WHO for those people working in high-risk exposure conditions i.e., in research or diagnostic laboratories, veterinarians, wildlife officers, animal rehabilitators and handlers. Research shows that children are at high risk exposure to rabies, therefore WHO also recommends vaccination of Children in highly endemic areas (Warrell 2012).

13.1. POST-EXPOSURE PROPHYLAXIS

Unfortunately, there is a lack of awareness in developing countries like Pakistan, Sri Lanka, Bangladesh etc (Dodet, Goswami et al. 2008). In Pakistan, private institutes use cell culture vaccines for PEP while rabies immunoglobulin (a life-saving biological agent used for PEP) is not available in any government institution because of its high cost (Chotani et al. 2004).

According to WHO Standards, the categorization of wounds after the bite will be helpful in further management. According to the severity of the bite it is categorized as category I: it is a non-bite and requires no PEP),category II: It is of moderate risk and skin integrity breaks, requires wound cleaning and vaccination, category III: high risk, multiple wound and provide rabies immunoglobulin and vaccination (Geneva 2005).

Two types of regimens are used for rabies PEP, first is the Modified TRC Regimen (intradermal application)which is mostly used in developing countries and is economical, the second is Essen regimen used intramuscular (WHO 2013).

The medical professional must be trained in the rabies wound classification and WHO-approved PEP protocols. Also, the provision of a free supply of rabies immunoglobulin and Cell culture vaccine should be ensured (Geneva 2005; Dodet and Bureau 2006).

The following are the guidelines of WHO for PEP (Organization 2000; Geneva 2005).

1. According to WHO recommendations instant and thorough washing of wounds with soap or any other detergent is recommended after a dog bite. If nothing is available then wash the wound extensively with fresh water.

2. WHO classified the RIG into three classes that have been made so far: ERIG (equine rabies immunoglobulins), HRIG (human rabies immunoglobulins), pERIG (highly purified equine rabies immunoglobulins). These RIGs should be administered at the wound site to neutralize the rabies virus before it affects the nerve endings.
3. Vaccination playsan important role in PEP.WHO recommended the use of a cell culture vaccine instead of a nerve tissue vaccine.
The primary goal in the twenty-first century is to increase cooperative efforts to eradicate canine rabies, which will reduce human fatalities (Banyard 2013). In many countries, canine rabies has been eliminated but in underdeveloped countries it is still present (Meslin and Briggs 2013).
The multidisciplinary approach should be the main emphasis of the strategy plan for eliminating canine rabies. It includes representatives from the governmental and private sectors, such as decision-makers, vaccine producers, veterinary professionals, researchers, and medical professionals (Taylor and Prevention 2013).
This collaborative multidisciplinary approach to combat rabies is also called the One Health Approach. It is an important step to combat rabies through mass vaccination and solicitous management of dogs (Attlan et al. 2011).

13.2. CULTURAL BELIEFS AND TRADITIONAL MEDICINES USED FOR RABIES

Globally, people have different beliefs and traditional medicines that are widely used to treat a variety of injuries and illnesses, including dog bites, and exposures that are risky for rabies. However, the beliefs and efficacy of most traditional remedies used for rabies prevention or treatment have not been demonstrated in controlled trials or proven in community-based surveys (Wallace et al. 2022).
In the first century A.D., the Roman scholar Celsus recommended that rabies was transmitted by the saliva of the biting animal. He incorrectly recommended keeping the patient underwater as a rabies treatment. The rabies killed those who did not drown. Other cruel treatments for rabies included using a hot poker and a "hair-of-the-dog" to burn open sores. In homeopathic medicine, the concept of *"similar,"* or *"like cures like,"* is used. The patient swallowed or applied rabid dog hair to the wound. While a hair-of-the-dog may cure a hangover, it did nothing to cure rabies. The usage of "mad stones" to treat rabies in 18thcentury America attracted the greatest interest. Mad stones are calcified hairballs that are discovered in ruminant animals' stomachs, including those of cows, goats, and deer. It was believed that they might extract the lunacy from the bite wound, rendering them therapeutic. Madstones was highly regarded and considered more valuable than rubies and were passed down through generations as '*family jewels*'. In 1805, a mad stone sold for $2000 in Essex County, Virginia (O'Niell 2017).
When a person or their animals are bitten by a dog in India, low-caste tribes adore the Hindu deity Hadkai Mata as the mother of Rabies. This concept might influence people's attitudes and behaviors about rabies prevention, even though it has never been studied. Hindus say that human rabies is typically the goddess's attempt to chastise disobedient individuals and improve interpersonal relationships. There is a basic understanding of the biochemical mechanisms of infection that result in rabies as a physical illness. If her victims go through the required phase of moral development, Hadkai Mata is thought to be able to heal rabies. Although there is no opposition to standard post-exposure prophylaxis, those who choose conventional treatment first usually put off getting it. The widespread vaccination of dogs has been greeted with some opposition since it is believed to interfere with the goddess's control over them by enraging, and sending them to bite wrongdoers. To effectively reduce dog rabies in this area, it is likely essential to address these cultural attitudes (Hampson et al. 2022).
Compared to 90% of persons in other countries, the majority of dog bite patients in Pakistan did not seek hospital care following a dog bite. This mindset and behavior significantly contribute to the rise of rabies-

related mortality in Pakistan. Additionally, it has been noticed that some people avoid going to hospitals in favor of traditional rabies cures and spiritual healers. Additional accounts of a prospective rabies patient seeking a spiritual healer in India and Africa exist. They may have investigated several spiritual healers, many of whom offer services at no cost. It is usual in Pakistan to send the victim to a spiritual leader or shrine after they have been bitten by a dog to receive blessings and take part in a "dam" (spiritual healing rite). As part of this procedure, the patient continues to receive spiritual care at the shrine across numerous visits spaced over a few weeks. If the patient's health doesn't get better in some situations, they might be isolated and kept away from other people. The patient unfortunately succumbs to his or her injuries in the end (Hussain et al. 2020).

Studies have shown how important multidisciplinary strategies are for containing and eradicating zoonotic illnesses like rabies. This includes the significance of comprehending various cultural and religiously mediated ways in which humans relate to animals; searching for points of agreement and mutual understanding; and developing context-tailored, linguistically accurate, locally acceptable, feasible, and effective strategies (Hampson et al. 2022).

14. CONCLUSION

The multifaceted nature of rabies demands a comprehensive approach encompassing epidemiology, pathogenesis, clinical presentation, diagnosis, and preventive strategies. Rabies, a disease with a history spanning over 4,000 years, continues to exert a significant toll on public health, particularly in Asia and Africa, where the majority of human deaths occur annually. The economic burden of rabies, estimated at over 4 billion dollars per year, highlights the urgency of addressing this neglected disease. The epidemiological landscape of rabies reflects a global presence, with over 95% of human deaths concentrated in Asia and Africa. India, China, and the Democratic Republic of Congo are particularly affected, demonstrating the need for region-specific interventions. In Pakistan, the endemic nature of rabies is exacerbated by inadequate medical training, low awareness, and a shortage of vaccines. The reliance on the indiscriminate killing of stray dogs as a preventive measure reflects a failure in controlling the disease.

Diagnostic methods, including the Direct Fluorescent Antibody Test (FAT), Polymerase Chain Reaction (PCR), and histopathology, play pivotal roles in confirming rabies. The importance of prompt post-exposure prophylaxis (PEP) cannot be overstated, as clinical symptoms signal an almost invariably fatal outcome. The lack of awareness in developing countries, such as Pakistan, underscores the need for education and accessible PEP, including rabies immunoglobulin and cell culture vaccines. Preventive measures, including vaccination programs and the One Health Approach, are vital for controlling rabies. Successful efforts in canine rabies control in developed regions serve as models for implementation in underdeveloped countries. Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) guidelines, as outlined by the World Health Organization (WHO), provide a framework for effective intervention.

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