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Review Article

Rabies: Understanding Neuropathology and Management

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ABSTRACT

Rabies is as old as antiquity, but the disease still remains an important public health problem. Rabies is the 10th biggest cause of death and occurs in more than 150 countries and territories. Among the diseases of viral origin, rabies is unique in its distribution and range of victims since it can afflict all warm-blooded animals. Over 90% of human deaths from rabies worldwide are caused by dog bites. Histologically, rabies is characterized by a viral encephalitis with intracytoplasmic accumulation of viral particles, called Negri bodies. The bases for neuronal dysfunction in rabies are complex, but they may involve degenerative changes involving neuronal processes such as dendrites and axons. Neuronal injury is greater in dorsal root ganglia than in CNS neurons. Permeability of the blood-brain barrier, proinflammatory cytokines, ion channels, neurotrophins, growth factors, neurotransmitters, vascular and immune cells are the major targets of the virus. Although understanding of the bases for neuronal dysfunction and neuronal death during virus infection has progressed, no fundamental abnormality has been identified so far. No effective therapy for human rabies is available and infection by virus is invariably lethal in the absence of protective measures. Incomplete understanding of pathophysiology of virus, insufficient vaccination campaigns and a wide biodiversity that increases the number of reservoirs of the rabies virus complicates the scenario. Mass vaccination, awareness campaigns along with the effective control of dog populations can be helpful in eradication of this dreadful fatal infection.

Key words: Anti-rabies vaccine, central nerve system, rabies, treatment, zoonosis.

INTRODUCTION

The World Health Organization recognizes rabies, an infectious disease of the central nervous system (CNS) with the highest fatality rate. [1] Rabies is an acute, progressive and fatal neuroparalytic viral disease of animal species. It is probably the oldest known zoonotic disease recognized for more than 5000 years. [2] Rabies is a viral meningoencephalitis anthropozoonotic infection caused by viruses from the genus Lyssavirus and the family Rhabdoviridae. [3]

Rabies is the 10th biggest cause of death due to infectious diseases worldwide. It is estimated that 2.5 billion people across 100 countries are at risk of contracting rabies. [4] Around 36% of these rabies related deaths occur in India. [5] According to WHO,

high death rate was experienced in India and lowest in Cambodia and Magnolia. [6]

Even by rudimentary surveillance, one person dies from the disease each 15 minutes, and more than 300 others are exposed. [7] Rabies continues to be an important public health problem, with about 75,000 human deaths per year, mostly in Asia and Africa. Sadly, many of the deaths occur in children. [8] Rabies is a serious public health and economic problem in India where dogs are responsible for about 97% of human rabies, followed by cats (2%), jackals, mongoose and others (1%). The animals which are mainly reported as causes of rabies are; dogs, raccoons, skunks, bats and foxes. [9] The disease is mainly transmitted by the bite of a rabid dog. [10]All mammals are susceptible to rabies, although canine rabies presents the greatest threat to humans, especially in Latin America, Asia and Africa. [11]

For a long time, this disease was classified into two main epidemiological cycles: urban rabies (meaning that dogs are responsible for the transmission and maintenance of the disease to humans), and wildlife rabies (in which the disease is maintained and transmitted by wild mammals. [12]

HISTORICAL PERSPECTIVE

The first statement reporting rabies was recorded in the pre-Mosaic Eshmuna Code of Babylon in the 23 rd century B.C. [13] The disease was variously known as lytta or lyssa, coming from the belief that the disease was caused by a worm under the tongue (lytta), or hydrophobia, which describes the thirst and fear of water associated with the disease. The present English name, rabies, comes from the Latin rabere, meaning raging, furious, savage, or madness, whereas the Greek term hydrophobia is now specifically used for rabies in man. [14]

It has been 129 years since Louis Pasteur's experimental protocol saved the life of a child mauled by a rabid dog, despite incomplete understanding of the etiology or mechanisms by which the miracle cure worked. [15] The disease has since been well understood, and highly effective vaccines are available, yet Pasteur's vision for ridding the world of rabies has not been realized. [16]

Aristotle noted the possibility of rabies transmission from an infected animal to a healthy one through a bite. Celsus coined the term "hudrophobia" (hydrophobia) and suggested that the saliva of a rabid animal contains a poisonous agent. Despite the long history of rabies, it was until 1769 that John Morgagni (1735–1789) (the father of pathological anatomy) theorized that the rabies virus spread itself through nerve fibers, not through veins. [17] In 1885, Louis Pasteur (1822–1895) developed the first successful vaccine against it. Then, in 1903, Adelchi Negri (1876–1912), an Italian pathologist and microbiologist, provided the first descriptions of virus-nerve cell interaction in the brains of rabies-infected animals. He detected cytoplasmic bodies (today called Negri bodies) in this group of nerves. About six decades later, in 1962, Soko-low and Vaney demonstrated that Negri's cytoplasmic bodies are in fact RNA granules embedded in a matrix of DNA. [18]

Although there are some rabies-free countries and islands, such as Greece, Portugal, Chile, New Zealand and Barbados, rabies is widely distributed throughout the world and is present on all continents. Despite continued attempts at medical intervention, rabies retains the dubious distinction of being the infectious disease with the highest case fatality ratio [19] and the number of cases have been increasing, mainly because there are a large global rabies reservoirs, in both domestic and wildlife animals. [20] Recently, a national

rabies survey in India, based on clinical diagnosis and sponsored by the World Health Organization, found that 20,000 persons died of rabies each year. [21] These observations indicate a great need to strengthen laboratory diagnostic capabilities for rabies in India and to use genetic typing to improve knowledge of the nature of the viruses that circulate in India. [22]

RABIES VIRUS

Rabies virus (RV) belongs to the genus Lyssavirus in the family Rhabdoviridae. [23] The virus is enveloped and has a single stranded, negative sense RNA genome [24] measuring approximately 60 nm × 180 nm. It is composed of an internal protein core or nucleocapsid containing the nucleic acid, and an outer envelope, a lipid- containing bilayer covered with transmembrane glycoprotein (G) spikes. It is an enveloped virus made up of lipoprotein over which numerous spikes are present. These spikes are made up of glycoprotein, which is necessary for attachment of the virus to receptors and hence determines the virulence of the virus. [25]

The virus genome encodes five proteins associated with either the ribonucleoprotein (RNP) complex or the viral envelope. The L (transcriptase), N (nucleoprotein), and NS (transcriptase associated, also called P protein) proteins comprise the RNP complex together with the viral RNA. These aggregate in the cytoplasm of virus-infected neurons form Negri bodies, the characteristic histopathological finding of RV infection. The M (matrix) and G (glycoprotein) proteins are associated with the lipid envelope. The N protein of RV plays vital roles in regulating viral RNA transcription and replication by encapsidating de novo-synthesized viral genomic RNA. [26]

RV M protein is a multifunctional protein, playing a crucial role in virus assembly and budding. M protein is responsible for recruiting RNPs to the cell membrane, their condensation into tightly coiled 'skeleton'-like structures and the budding of enveloped virus particles. [27] Recently, there has been evidence that M is a key factor in the regulation of RV polymerase functions that exerts opposite effects on transcription and replication, and thereby tips the balance toward replication. [28]

Replication is characterized by production of a full-length positive RNA strand complementary to the entire parental template, followed by production of full-length negative- strand RNAs. Unlike transcription, replication requires active, ongoing translation, particularly of viral N and P proteins. After synthesis of N, P and L proteins, association of these proteins in the cytoplasm with newly replicated genomic RNA occurs to form the ribonucleoprotein core. The M protein associates with the core forming a coiled structure called skeleton, condenses the RNP core in the cytoplasm and binds cores to the membrane in preparation for budding. [23] The G protein spikes bind the cell surface receptors and antibody binding sites and any variation in the gene encoding for this protein may affect the pathogenic and immunogenic properties of the virus. [29] It interacts with internal virion components, most likely the M or N proteins, and subsequent envelopment of the particles leads to the last phase of the infection cycle, which is budding, releasing the virus for new infections. [23]

PATHOGENESIS

The most frequent way by which humans become infected with RV is through the bite of infected dogs and cats and other wild carnivorous species beside insectivorous and vampire bats. Cattle, horses, deer and other herbivores can become infected with rabies and although

they could transmit the virus to other animals and man, this rarely occurs. [7]

The infection occurs by inoculation of the virus into the bite wound through the saliva of the infected animals. The receptors for rabies virus include nicotinic acetylcholine receptors, neural cell adhesion molecules (NCAM), and nerve growth factor receptors. There is an initial multiplication of the virus in the local musculature and spread via motor or sensory nerves to the spinal cord and brain. Rabies virus binds to nicotinic acetylcholine receptors at the neuromuscular junction. The virus travels towards the central nervous system (CNS) within motor and sensory axons by retrograde fast axonal transport at a rate of 12-100 mm per day. [30]

The virus enter the peripheral nervous system via the neuromuscular junctions, and moves rapidly centripetally to the central nervous system, particularly to the nearest sensory or motor neuron in the dorsal root ganglion or anterior horn of the spinal cord where it replicates. [31] In rabies there are mild inflammatory changes in the central nervous system. Neurons predominantly infected by the rabies virus, and there are few degenerative changes in neurons. Infected neurons may contain eosinophilic inclusions in the cytoplasm, called Negribodies which are most prominent in large neurons (eg, Purkinje cells) and ultrastructurally are composed of large aggregates of granulofilamentous matrix material and variable numbers of viral particles. [32]

Once virus reaches the brain, there is extensive replication involving every region. At the later stage of infection, RV can be transported centrifugally to many peripheral tissues and organs, such as respiratory tract, cornea, skin of the head and neck, adipose tissue, adrenal medulla, and renal parenchyma. Extremely high viral titers are directly reached by way of efferent secretory nerves to a primary exit portal, the acinar cells of the salivary glands, often exquisitely timed to host aberrant behaviors which enhance rabies shedding potential and its natural perpetuation. [33] Despite wide-spread replication, there are not many observable pathological changes in the brain except for the presence of Negri bodies. Recent evidence indicates that neuronal apoptosis could play a role in the pathogenesis of the disease. [34] Other factors that could contribute to the disease process may be abnormalities in neruotransmitters, accumulation of nitric oxide and pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α). [35]

Recent evidence has shown that the rabies virus phosphoprotein interacts with the cytoplasmic dynein light chain [6] which is an important component of the microtubule based transport system; it is not clear whether this alone accounts for the viral transport mechanism. After infection develops in spinal cord or brain stem neurons, rabies virus disseminates rapidly throughout the central nervous system by fast axonal transport along neuroanatomical connections. Under natural conditions, rabies virus infection of the CNS causes only relatively mild neuropathological changes without prominent evidence of neuronal death. Together, these observations have led to the concept that the neurological disease in rabies must result from neuronal dysfunction rather than neuronal cell death.

Studies of neuronal dysfunction have revealed electroencephalo-graphic abnormalities, including the disappearance of rapid eye movement sleep and the development of pseudoperiodic facial myoclonus. Brain electrical activity terminated about 30 min before cardiac arrest, indicating that cerebral death in experimental rabies occurs prior to failure of vegetative functions. [37]

RV infection of neurons also induces dysfunction of ion channels, for example, reduction in sodium channels and inward rectifier potassium channels, [38] which could prevent infected neurons from firing action potentials and generating synaptic potentials, resulting in functional impairment. Decreased binding of serotonin (particularly the subtype 5-HT 1D) to its receptors has also been reported. [39] Recent studies of the release of norepinephrine, dopamine, and serotonin in the hippocampi of rats infected with RV indicated that at the terminal stage of the disease neurons are no longer capable of releasing neurotransmitters at the synaptic junctions. [40] Hence, there is evidence of impaired release of neurotransmitters and binding of neurotransmitters to the receptors, which may result in neuronal dysfunction in patients infected with rabies. Although there is extensive RV antigenic involvement throughout the CNS, there is an overall paucity of gross and histopathologic lesions attributed to rabies. In general, gross examination of the brain shows mild congestion of the meningeal vessels and the spinal cord presents frequently focal congestion of parenchymal and meningeal vessels. [34] Microscopic examination usually demonstrates slight perivascular cuffing, limited tissue necrosis, acidophilic intracytoplasmic neuronal inclusions, and rarely neuronophagia. [41] Electron microscopic examination of the brain stem of rabies- infected raccoons revealed accumulation of electron dense material within neuronal perikarya. [42] Light and electron microscopic examination indicated that the accumulated intracellular material had high lipid content and studies of the central nervous system of mice, dogs and cats infected with a RV strain isolated from a European bat showed neuronal cytoplasmic changes considered to be a form of spongiosis. [43] A variety of studies of RV infection in experimental animals and in vitro have provided evidence in neurotransmission involving acetylcholine, serotonin and γ-amino-n-butyric acid (GABA). [35] Furthermore, infection with silver haired bat rabies virus resulted in the down regulation of several proteins that were relevant to synaptic physiology. Furthermore, the down regulation of these proteins can block synaptic vesicles from docking and fusing to the plasma membrane; therefore, the release and uptake of neurotransmitters is reduced. [44]

Most recently, the structural alterations of neuronal processes in mice were investigated after mice were infected with RV. Silver staining of infected brain sections showed severe destruction and disorganization of neuronal processes in mice infected with pathogenic RV but not with attenuated RV, suggesting that pathogenic RV causes degeneration of neuronal processes possibly by interrupting cytoskeletal integrity. Nevertheless, the significance of all of these findings is uncertain because no fundamental defect has yet been found explaining neuronal dysfunction in natural rabies. [37] Despite all the effort and advances in the knowledge of rabies, the true causes of the beginning of the symptoms and the eventual mortality of rabies are still not well understood.

ANIMAL CHARACTERSTICS AND EXCRETION OF VIRUS

Clinical diagnosis of rabies divided upon three stages; prodromal, excitement (furious) and paralytic (dumb). But all these stages cannot be observed in an individual. [45] The very first clinical symptom is neuropathic pain at the site of infection or wound due to viral replication. Following by the prodromal phase either or both the excitement or paralytic forms of the disease may be observed in the particular species. It is also documented that cats are more likely to develop furious rabies than dogs. In some

cases, no signs are observed and rabies virus has been identified as the case of sudden death. [46] Diagnosis can only be confirmed by laboratory tests preferably conducted post mortem on central nervous system tissue removed from cranium. [47] Tests are also performed on the samples of saliva, serum, and skin biopsies of hair follicles at the nape of the neck. [48]

Although three distinct phases of the disease often are described, they are not always observed. Each phase has a different set of outward, or visible, symptoms. The first ("prodromal") phase occurs early during the illness. At this stage, the virus is replicating and begins to pass through the nervous system. Behavioral changes, often in the form of a reversal of normal patterns, usually begin to show in this phase. For example, if an animal usually is shy, it may become more aggressive following infection, whereas a more aggressive animal under normal conditions may become more timid. In wild animals particularly, those that normally would be expected to be active during the day (diurnal) become active at night, and nocturnal animals, such as raccoons and bats, are observed moving about more than expected during the day. During the prodromal phase, the dog's behavior may change. Aggressive and high-strung dogs may become more affectionate than usual and ordinarily friendly dogs may become shy and seek secluded areas or become snappy and irritable. The dog's temperature may rise slightly, the pupils may dilate and the nictitating membrane may cover the eye. The dog may also salivate excessively.

In the second ("furious") phase, the animal becomes extremely irritable and aggressive, often lunging at or biting anything that moves near it. In fact, the word rabies is derived from the Latin term for rage or fury. Additionally, infected animals may produce excessive amounts of saliva during this stage, from which the expression "foaming at the mouth" is derived. However, not all infected animals outwardly display the "furious" stage and may not show any aggression at all. Fever is common, and signs of autonomic dysfunction, including hypersalivation, sweating, piloerection, and priapism may be present. About 50%–80% of patients develop hydrophobia, which is the most classical clinical manifestation of rabies. Patients may initially experience pain in the throat or have difficulty swallowing on attempts to swallow; they experience contractions of the diaphragm and other inspiratory muscles, which last for about 5-15 seconds. Subsequently, the sight, sound, or even mention of water (or any liquids) may trigger the spasms. A draft of air on the skin may have the same effect (aerophobia). The disease may progress through paralysis, coma, and multiple organ failure, and eventually it causes death. Encephalitis caused by other viruses is generally associated with earlier impairment of consciousness with less prominent early evidence of brain stem involvement. [7] During excitable (Furious phase) in dogs signs of the disease are most easily recognized. The dog becomes severely agitated and restless and sometimes gets an urge to roam. The dog is most dangerous at this stage because of its urge to bite anything it encounters. In most cases, an altered phonation (a characteristic high pitched bark) develops, caused by paralysis of laryngeal muscles. The dog has difficulty in swallowing because of spasms and paralysis of the pharyngeal muscle, causing the animal to drool. If the dog does not die during one of the characteristic convulsive seizures, the disease usually progresses to muscular incoordination, paralysis, coma, and death.

The final ("dumb") stage is manifest by the onset of paralysis, most often in the

lower jaw and extremities. Hence, this stage also is known as the "paralytic" phase. Individuals eventually lose the ability to chew and swallow, walk normally, right themselves when they fall, maintain a standing position, or, in the case of bats, maintain flight. The term hydrophobia, which many people call this disease instead of rabies, comes not from an animal's fear of water, but from its inability to drink or swallow water and hence its avoidance of water. Death usually follows the development of these "dumb" symptoms. In paralytic rabies, flaccid muscle weakness develops early in the course of the disease, often beginning in the bitten extremity and spreading to the other extremities and facial muscles. Sphincter involvement, pain, and sensory disturbances also occur. Hydrophobia is unusual, although Patients infected with RV develop severe agitation, depression, hydrophobia, and paralysis followed by impaired consciousness and coma. [19] Patients eventually die of circulatory insufficiency, cardiac arrest, and respiratory failure [49] and respiratory muscles become involved later in the course of the illness. Patients with paralytic rabies usually survive longer than patients with the encephalitic form of disease. Paralytic rabies may be misdiagnosed as an inflammatory polyneuropathy (e.g., Guillain-Barré syndrome) or a spinal cord disorder. [7] Dumb rabies in dogs occurs when the excitable phase is extremely short or absent. The most characteristic sign is the "dropped jaw" caused by paralysis of the masseter muscles. The animal often makes choking sounds as if a bone were stuck in its throat. Attempts to remove this "bone" often result in owners scratching their hands on the dog's teeth and being exposed to the disease. [50]

The particular time of salivary virus excretion before sickness is crucial, since transmission may occur when the animal appears normal and no preventive measures are taken. The failure to appreciate the significance of such normally acting but infective animals can result in delayed diagnosis and possible fatal results in those persons exposed. Rabies virus is usually present in the saliva when clinical signs appear, but in some studies prior to 1970 rabies virus was also demonstrated in the saliva of dogs 3 - 6 days before clinical signs appeared. [51]

CLINICAL ASPECTS: TREATMENT AND DIAGNOSIS

Once an individual is infected with the rabies virus, it replicates within the cytoplasm of muscle cells and can pass from cell to cell. Eventually, it reaches nerve receptors and enters the nervous system. The virus passes along the nerve network, traveling to the central nervous system, where it concentrates in the brain and upper spinal cord. As the disease progresses, the virus continues to multiply and spreads back through the peripheral nervous system to the salivary glands. Although the virus is known to exist in other parts of the body (e.g., the skin and intestines), it is found in amounts too small to play a role in transmission. Symptoms in animals and humans can be similar, but usually are highly variable and numerous.

In humans, initial symptoms typically appear within 30 to 60 days following exposure and can include pain and itching at the site of the virus' entrance into the body, restlessness, headache, fever, nausea, sore throat and loss of appetite. Increased production of saliva, muscle stiffness, sensitivity to light or loud sounds, irrational excitement, or convulsions occurs as the infection progresses. Other symptoms may develop later, such as anxiety, confusion, agitation, delirium, and the display of abnormal behavior. Symptoms of rabies in animals can include an evident change in behavior, loss of appetite, fever, change in phonation (e.g., the sound of a

dog's bark), greater excitement, aggression, paralysis (especially in the lower jaw), and increased salivation.

The interval between inoculation and the onset of symptoms is between 3 weeks to 3 months but may prolong up to years. In general the nearer the bite is to the head, the shorter the incubation period. The illness may have a short prodrome characterized by itching or paraesthesia of the healed bite wound (40%) and other non specific features.

Treatment with passive immunity for the rabies is effective only when the patients have not shown the central nerve system (CNS) signs. Vaccines have been well developed for the prophylaxis of the disease. When individuals are infected with rabies, early post-exposure prophylaxis (PEP) treatment may avoid death. Unfortunately, the PEP treatment is deemed ineffective once the clinical signs have appeared. The mortality is almost 100% once clinical signs were observed, although few cases can survive successfully after the onset of symptoms. [52]

Patients infected with RV develop severe agitation, depression, hydrophobia, and paralysis followed by impaired consciousness and coma (19). Patients eventually die of circulatory insufficiency, cardiac arrest, and respiratory failure. [49]

Though rabies is a 100 per cent fatal disease, it is100 per cent preventable if state of the art modern prophylactic treatment is instituted soon after the exposure. The WHO has given clear cut guidelines on the categorization of exposures, wound management, active immunization with vaccines and passive immunization with rabies immunoglobulins (RIG). All these three parameters are equally important. More than a decade ago, in most parts of the world, nerve tissue vaccines have been replaced by highly potent and safe cell culture vaccines like human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCEC, Rabipur), and purified vero cell rabies vaccine (PVRV, Verorab). However, in India use of outdated and WHO banned vaccine still continues. It is only recently that efforts have been made by Central Government to phase out this vaccine and replace with modern cell culture vaccines. [53]

For full protection, 5 doses of these vaccines are to be administered on days 0, 3, 7, 14 and 28. In all category III exposures, local infiltration of calculated doses of RIG is very essential. Many cases of rabies have occurred despite full course of vaccination but without passive immunization. In order to economize the administration of cell culture vaccines and to make it more affordable, WHO has advocated abbreviated intradermal (ID) regimens, Two types of ID regimens are approved by WHO, viz., the 2 site regimen also known as Thai Red cross regimen (TRC, 2-2-2-0-1-1) in which 0.1 ml of vaccine is given ID over deltoids at 2 sites on days 0, 3, and 7 and at one site on days 28 and 90; the multiple site regimen (Oxford regimen) consists of giving 0.1 ml vaccine ID at 8 sites on day 0, at 4 sites on day 7, and at one site on days 28 and 90. Both regimens are effective in producing adequate neutralizing antibody titres. [25]

Post-exposure prophylaxis

Bite by all warm blooded animals necessitates post-exposure prophylaxis. As rabies is practically 100% fatal, bites by dogs and cats in particular must be considered as a "medical emergency" and the "life-saving" post exposure prophylaxis must be provided immediately.

If a person is bitten by an animal, the wound and scratches should be washed thoroughly with soap and water to decrease the chances of infection. Post-expo-sure prophylaxis involved one dose of rabies immunoglobulin and five doses of rabies vaccine within the 28 days period. Rabies

immune globulin contains antibodies from blood donors who were given rabies vaccine. The rabies vaccine works by stimulating a person's immune system to produce antibodies that neutralize the virus.

Schedule for post-exposure vaccination

Traditionally, modern cell culture vaccines are given intramuscularly. The vaccines should not be administered in the gluteus muscle to avoid injury to the sciatic nerve and to lessen the delivery of vaccine to the adipose tissue. [54]

Two regimens are used:

a. Classic 5 dose intramuscular regimen (Essen regimen) in which one dose of vaccine, i.e., 1 ml of HDCV, PCECV or 0.5 ml of PVEV is administered on day 0, 3, 7, 14, and 28.

b. Alternate 2 - 1 - 1 regimen in which 2 doses of vaccine are given on both deltoids on day 0 and then one dose each on day 7 and 21 11 .

Since the cell culture vaccines are very expensive, developing countries like India cannot afford the universal use of cell culture vaccines as recommended by the WHO 11. If Rabipur Tm (PCECV) is used then the annual cost would be approximately Rs. 8.7 billion. The WHO therefore recommends the use of cell culture vaccines by intradermal route. Intradermal vaccination reduces the volume of vaccine required and the cost of vaccination by 60 - 80% 11. The efficacy and immunogenicity of the intradermal regimen has been established by various studies in Thailand, Sri Lanka and India (25). However, certain precautions are required that include proper staff training, use of appropriate 1 ml syringe and short hypodermic needles. Two regimens are used, the 8 site Oxford regimen and the 2 site Thai Red Cross regimen. [55]

Pre-exposure prophylaxis

Pre exposure vaccination is recommended to people at continued risk such as veterinarians, laboratory persons, dogcatchers, forest officials, etc. All these groups should be treated with rabies vaccines to avoid the chances of sudden infection. Only cell culture vaccines should be used. The recommended schedule is 1 dose of vaccine intramuscular (im) on days 0, 7 and 28. Pre exposure vaccination of children in India (at least on voluntary basis) should be encouraged, as these constitute nearly 60 per cent of human rabies deaths. In spite of great advances in virology, there is as yet no treatment for rabies. [9,25]

Schedule for pre-exposure vaccination

Pre-exposure vaccination simplifies the management of subsequent exposure as fewer doses of vaccine are required and rabies immunoglobulin is not required. Three doses of vaccine are given on day 0, 7, and 28 by intramuscular route. Alternatively, 0.1 ml of HDCV may be injected intradermally also 24. Of note here is the interference of chloroquine with the immune response of anti-rabies vaccines. So HDCV should not be given intradermally if the person is receiving chloroquine. The need for booster vaccination may be monitored by serologic testing performed every six months to 2 years and booster dose is given when titres fall below 0.5 IU/ml. [56,57]

CONTRAINDICATIONS AND PRECAUTIONS

As rabies is nearly 100% fatal disease, there is no contraindication to PEP (Post-Exposure Prophylaxis (PEP). Pregnancy, lactation, infancy, old age and concurrent illness are no contra indications for rabies PEP in the event of an exposure. PEP against rabies takes preference over any other consideration as it is a lifesaving treatment. Moreover, rabies vaccine does not have any adverse effect on pregnant woman, course of pregnancy, fetus or lactating mother. Hence, complete PEP should be given depending on the category

of the exposure. People taking chloroquine for malaria treatment or prophylaxis may have a reduced response to ID rabies vaccination. These patients should receive the rabies vaccine intramuscularly. As with all other immunizations, vaccinated persons should be kept under medical supervision for at least 15–20 minutes following vaccination. Previous reaction to any component of a vaccine is a contraindication to the use of the same vaccine for PEP or PrE (Pre-Exposure Prophylaxis (PrEP)).

CONCLUSION

It is unfortunate that in spite of availability of effective vaccines and sera, rabies takes such a heavy toll of lives in India and other Asian countries. Rabies is controlled to a great extent in neighboring countries like Thailand, Sri Lanka and Philippines and many countries around the globe have gained the status of rabies free territories. This shows that rabies can be successfully ruled out from the high-risk areas by taking preventing measures. The advent of scientific medicine also makes rabies control possible. Public awareness in this regard can play a major role and change of lifestyle to avoid these kinds of viral diseases. Combined efforts from medical and veterinary fraternity can help to evolve strategies not only to prevent human rabies deaths but also to plan future actions to bring down incidence of canine rabies.

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