Human rabies: a disease of complex neuropathogenetic mechanisms and diagnostic challenges

Thiravat Hemachudha, Jiraporn Laothamatas, and Charles E Rupprecht

Rabies is inevitably fatal and presents a horrifying clinical picture. Human rabies can manifest in either encephalitic (furious) or paralytic (dumb) forms. The brainstem is preferentially involved in both clinical forms, though there are no clinical signs of brainstem dysfunction. Differences in tropism at the inoculation site or the CNS, in the route of spread, or in the triggering of immune cascades in the brainstem may account for clinical variation. Rabies still poses diagnostic problems, particularly the paralytic form, which closely resembles Guillain-Barré syndrome, or when a patient is comatose and cardinal signs may be lacking. Molecular methods allow reliable detection of rabies-virus RNA in biological fluids or tissue before death. Deviations from the recommendations on prophylaxis of the World Health Organization lead to unnecessary loss of life. To date, attempts to treat human rabies have been unsuccessful.


Rabies is an acute encephalitis caused by viruses of the genus Lyssavirus, of seven putative genotypes. Classic rabies virus accounts for most cases. The disease is not notifiable in most of the less developed countries, and it is widely perceived by public-health officials as rare and unimportant in many regions, especially Asia. Compounding this ignorance, the World Health Organization (WHO) ranks rabies low on its priority lists.1 A worldwide total of 32 451 human deaths in 1998 (at least 30 000 in India alone) is a gross underestimate.2 For example, the projected rate in Pakistan, with a population 10% that of India, is believed to be at least 5000 deaths annually.3 At present, rabies kills more people than yellow fever, dengue fever, and Japanese encephalitis.4 More than 7 million people worldwide received postexposure treatment in 1998.2 The situation in the less developed countries is exacerbated by poor community participation in local control programmes, cultural and religious beliefs, a lack of social awareness, and limited access to biological agents. More importantly, there is no political commitment towards rabies prevention and control. Unreliable epidemiological data are related to limitations in diagnostic laboratories and the complexity of disease manifestations. With rapid movement of people and animals, cases can appear in regions where rabies has been eliminated or never recorded.

Clinical symptotamology is complex and commonly causes confusion to physicians. Therefore, all health-care providers, particularly neurologists, should diagnose and differentiate rabies from other diseases and understand the basic principles of the administration of prophylaxis.

In this review, we concentrate on clinical features of human rabies, its pathophysiology, and diagnostic methods. Other features of rabies are reviewed in The Lancet Infectious Diseases.4

Vector transmission

Transmission from dogs is the most common cause of rabies. In Thailand, almost all of the average 70 deaths per year are attributable to dog bites (figure 1). Of 10 million dogs in Thailand (650 000 in the city of Bangkok alone), most are semirestricted community dogs (living in public areas and fed by the local population); for these animals, immunisation and population-control programmes could be effective.1 In more developed countries with adequate

---

**Figure 1.** The dog is the principal reservoir and vector for transmission of rabies to human beings.

---

TH is Professor of Neurology at the Department of Medicine, Chulalongkorn University Hospital, and JL is Assistant Professor of Neuroradiology at the Department of Radiology, Ramathibodi University Hospital, both in Bangkok, Thailand. CER is the Chief of the Rabies Section, Viral and Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA.

**Correspondence:** Professor Thiravat Hemachudha, Neurology Division, Department of Medicine, Chulalongkorn University Hospital, Rama 4 Road, Bangkok 10330, Thailand. Tel +662 256 4333 ext 3573; fax +662 252 7858; email th-cu@usa.net

Canine vaccination and surveillance, emerging animal reservoirs include various species of wild animals. Bats account for less than 10% of animal rabies cases reported in the USA and Canada, but during the past 20 years variants of bat rabies virus became the most common cause of human death from rabies. These viruses were identified in 27 of 42 patients, 23 during 1980–2000, but only two patients provided a definite history of bat bite. Moreover, Australia, previously free of rabies, became an endemic area in 1996, when a new pteropid lyssavirus was found in flying foxes (genus Pteropus) and other bats, including insectivorous species. In November 1996, the first human being with rabies associated with this virus died after bat exposure, and a second person had rabies-like encephalitis after an incubation period of 27 months.

**Clinical features**

Rabies mortality after untreated bites by rabid dogs varies from 38% to 57%, depending on the severity and location of the wound and presumed virus concentration in the saliva. Exposure to rabid animals of other species, such as wolves, may result in 80% mortality. Bites on the head, face, neck, and hand, particularly with bleeding, carry the highest risk and are generally associated with a shorter incubation period. Nevertheless, all bites should be treated with the same urgency. In the case of rabid bats, risk is present even after a superficial bite, owing partly to the unique ability of these agents to replicate in the epidermis and dermis.

Clinical features can be divided into five stages: the incubation period; the prodrome; the acute neurological phase; coma; and death. Because of the clinical diversity during the acute neurological phase, rabies can be distinguished as classic (encephalitic or furious and paralytic or dumb forms) and non-classic forms. Encephalitic and paralytic rabies also differ in the morbidity period (interval between clinical onset and death) and immunological features.

Classic rabies is almost always associated with true rabies virus (genotype 1). Non-classic rabies patterns can be found in patients exposed to bats and, lately, in Thai patients infected by dogs. Atypical presentations are also seen in rare rabies survivors.

**Incubation period**

The incubation period of rabies is the most variable among viral infections of the CNS; the commonest period is 1–2 months but the range is from less than 7 days to more than 6 years. Unusually long incubation periods of at least 27 months, 4 years, and 6 years were associated with Australian bat lyssavirus infection and have been found in immigrants to the USA from southeast Asia. An incubation period of less than a week has been seen with direct inoculation of the virus into nervous tissue, as in patients who sustain brachial-plexus injury from dog bites. The absence of a history of exposure to a rabid animal, however, cannot exclude rabies, particularly in rabies-endemic areas where exposures are common, especially when such contact is deemed trivial.

**Prodrome**

The prodromal stage begins when the virus moves centripetally from the periphery to dorsal-root ganglia (causing neuropathic pain) and to the CNS. These developments mark the end of the incubation period, and most patients die within the next 2 weeks. At this stage, symptoms are vague, variable, and non-specific. However, as many as a third of patients with dog-related infections (equally common in encephalitic and paralytic rabies) and three-quarters of those with bat-related disease experience local symptoms or neuropathic pain at the bite site presumably due to ganglioneuronitis, described as burning, numbness, tingling, itching, or pruritus. An intense and progressive local reaction, starting at the bite site and gradually spreading to involve the whole limb in a non-radicular pattern, or the ipsilateral side of the face, is a reliable indicator of rabies. Pruritus commonly results in extensive excoriation (figure 2). Rarely, these symptoms can occur at locations remote from the bite site. Prodromal symptoms last a few days, generally not more than a week.

**Acute neurological phase**

**Classic rabies**

During the acute neurological phase, objective signs of nervous-system dysfunction begin. Mental dysfunction can be seen in patients with encephalitic rabies as well as in some with paralytic forms, but to a much greater degree in the encephalitic group. Non-classic rabies variably manifests without any distinct characteristics. The features can resemble those in patients with enterovirus-71 infection, Japanese encephalitis, or Nipah-virus infection.

Two-thirds of patients with classic rabies have an encephalitic form, and the remainder present with paralysis. Most patients with the encephalitic form die within 7 days (average 5 days) of onset, and the average survival period is about 2 weeks in paralytic cases.
attention span may be shortened. Within 24 h, three major cardinal signs follow: fluctuating consciousness; phobic or inspiratory spasms; and autonomic stimulation signs. Mental status alternates between normal periods and progressively more severe agitation and depression. Irritability is gradually followed by deterioration of consciousness and coma.

Phobic spasms are seen in all patients with encephalitic rabies at some stage, but they are not elicited once drowsiness and coma supervene. Phobic spasms, aerophobia, and hydrophobia can be incited by blowing or fanning air on the face or chest wall, by encouraging the patient to swallow, or by merely offering a drink. Aerophobia and hydrophobia may appear in isolation. The startle reaction results from spasms of the accessory neck muscles and diaphragm followed by neck flexion (or rarely by neck extension). During the induced spasms, patients may display fearful facial expressions. These may not be associated with laryngeal or pharyngeal spasms. However, when these are evident, the patient may spit abundant saliva. Phobic spasms cannot be explained by a conditioned reflex. Many patients have the first hydrophobic attack while taking a bath with no previous swallowing difficulties or pain on swallowing. Soft-palate and pharyngeal sensations remain intact, but the gag reflex is hyperactive. Inspiratory spasms are similar to phobic spasms, but occur spontaneously without stimulation, are less intense and infrequent while the patients are fully alert, and may be identified once coma supervenes. Opisthotonos, a characteristic sign of tetanus, is extremely rare.

Definition of autonomic dysfunction aids diagnosis. Hypersalivation is a unique feature. During the confusion-agitation state, there may be transient reactions of fixed, dilated, or constricted pupils, anisocoria, localised (on the bitten limb) or generalised piloerection, neurogenic pulmonary oedema (though only in three cases among more than 170 patients in our experience), excessive sweating, priapism, and spontaneous ejaculations.

In classic encephalitic rabies, cranial-nerve deficits may not be detected. Hemitract signs, such as hemiparesis or hemianesthesia, are not present. Seizures are rare as presenting manifestations but are occasionally seen in the preterminal phase.23

**Paralytic (dumb) rabies**

This form of the disease is extremely difficult to diagnose owing to the lack of aggression. The major cardinal signs appear late and are not prominent. Phobic spasms occur in about 50% of patients. Inspiratory spasms are less evident because of weakness; they generally start in the bitten limb but progress to all limbs and the bulbar and respiratory muscles. Facial diparesis is as common as in sporadic Guillain-Barre syndrome (GBS). In patients with facial bites, weakness may initially involve ipsilateral facial and oculomotor muscles. There is no relation between the development of encephalitic or paralytic rabies and the site of the bites.22 Presentations mimicking ascending paralysis, with loss of joint position sense and hypoaesthesia to pinprick at the thoracic level, are extremely rare.23

The following features suggest paralytic rabies and serve to differentiate this disorder from GBS: persistent fever from the onset of limb weakness; intact sensory function of all modalities except at the bitten region; percussion myoedema; and bladder dysfunction.24 Percussion myoedema is most readily elicited on the chest, deltoid, and thigh regions; it consists of mounding of the muscle at the percussion site, which then disappears over a few seconds (figure 3).24 The reason why percussion myoedema is associated with paralytic rabies is unknown, but this sign is not observed in GBS or encephalitic rabies, or in neuroparalytic accidents after neural-tissue vaccination. However, it has to be interpreted with caution, because it can be found in extreme cachexia, hyponatraemia, and the syndrome of inappropriate secretion of antidiuretic hormone, hypothyroidism, and renal failure.

**Non-classic rabies**

Patients with bat-related rabies are reported to have clinical features substantially different from those of dog-related cases.5–8,12,15,25–28 In addition to neuropathic pain, which is much more common,5,12,15,28 there are reports of radicular pain, objective sensory or motor deficits, and choreiform movements of the bitten limb during the prodromal phase. Both focal brainstem signs and myoclonus are common. Other patients have been described as having hemiparesis or hemisensory loss, ataxia, vertigo, or Horner’s syndrome. Convulsive and non-convulsive seizures and hallucinations are frequent. In the USA, where about 50% of cases before 1996 were associated with bats, phobic spasms were found in half of these patients but were described in only one of six bat-related cases during 1997–2000.5,6

Non-classic presentations have been noted in at least six patients with dog-related rabies since 1997 at Chulalongkorn University alone.25 One manifested with ocular myoclonus and hemichorea. Other patients had nocturnal agitation but remained calm during the day; other symptoms and signs included repeated spontaneous ejaculations, paraparesis, and facial and bulbar weakness with preserved arm strength or bilateral arm weakness. No patient had phobic spasms or autonomic hyperactivity.
Coma
Inspiratory spasms may be useful in diagnosis at this stage. However, they are difficult to detect in paralytic rabies because of weakness. Sinus tachycardias, disproportionate to fever, are observed in most cases even when hydration is adequate. These events are followed by a nodal rhythm, and in some cases, by supraventricular and ventricular arrhythmia.32 Before or at the time of hypotension, echocardiography shows reduction of the ejection fraction in almost all cases.15 Viral involvement at the sinus or atrioventricular node and myocarditis are likely mechanisms.9 Coma precedes circulatory insufficiency, a prime cause of death, in almost all cases. Haematemesis is seen in 30–60% of patients 6–12 h before death.29

Recovery
Rare rabies survivors had atypical presentations.15 The first patient (1972), who was exposed to a rabid bat, had unsteady gait, dysarthria, and hemiparesis.31 The second (1976), exposed to a rabid dog, had quadriaparesis and generalised myoclonus at the early stage and later developed cerebellar signs (ataxia, dysmetria, and dysdiadochokinesia), frontal-lobe signs, and bibrachial weakness.33 The third case (1977) had aerosol exposure to a highly concentrated fixed rabies-virus strain.31 Between 1992 and 1995, four other cases of recovery from rabies were reported in Mexican children.34 Three were bitten by rabid dogs and one by a vampire bat. Each received prophylaxis promptly with cell-culture vaccine but not rabies immunoglobulin. All the children developed encephalitis within a month of exposure, with high concentrations of neutralising antibodies to rabies virus detected in the CSF. Acute signs persisted for months and there were chronic sequelae.

Pathogenesis
Exposure
Almost all cases of human rabies are caused by a bite from a rabid animal. Efficient transmission depends partly on the severity of the bite, particularly if it is deep enough to reach muscles, at areas where the muscle tissue may contain a high density of nicotinic acetylcholine receptor, as well as the amount of virus in the saliva.35 The risk of rabies acquisition is at least 50 times higher with a bite than with scratches (5–80% vs 0.1–1.0%).49 However, bite severity may not be critical in bat-related and so-called cryptic rabies, in which a typical history of exposure to a bat is rarely obtained.44–46 Although non-bite exposures are extremely unusual causes of human rabies, contamination of an open wound, a skin abrasion, or the conjunctiva, oral mucous membranes, or genitalia with the saliva of rabid animals also carries a risk of the disease.48 Rarely, rabies can be acquired via inhalation of aerosolised virus in caves inhabited by millions of rabid bats and in laboratory accidents with infected aerosolised tissues.33,34 Transmission is also possible by handling and skinning of infected carcasses.29,30 Human-to-human transmission other than by corneal transplantation has not been well documented,41 although there is a potential risk from contact with patients since secretions commonly contain viable virus.54,40 Transplacental transmission has been reported infrequently, with no defining mechanism. Infants born to mothers with encephalitic rabies were found to be healthy.14

Transit to the CNS
Once rabies virus is successfully inoculated into wounds, the initial infectious event may depend on the lyssavirus genotype. In the case of canine rabies virus, the viral glycoprotein may bind to nicotinic acetylcholine receptor on the muscle16–18 whereas in the case of some bat lyssaviruses, the virus may bind to unknown receptors in the epidermis or dermis.11

Another characteristic is the long incubation period or eclipse phase, which may be explained partly by localisation of virus within the muscle or other cells at the neuromuscular junction. Studies in skunks showed that rabies-virus antigen and genome could be demonstrated as long as 2 months after inoculation into muscle.44 In certain circumstances, this persistence may provide an opportunity for host immune clearance and for postexposure treatment.44,45

After budding from the plasma membrane of muscle cells, virus is taken up into unmyelinated nerve endings at the neuromuscular junctions or at the muscle spindles. Rabies virus is transported to the CNS via retrograde axoplasmic flow, which can be blocked by colchicine or vinblastine injection.44 The virus then infects and replicates again in the dorsal-root ganglia and anterior-horn cells.51,52 At the dorsal-root ganglia, viral replication may be recognised and attacked by immune effectors, resulting in ganglioneuritis and a clinical prodrome of neuropathic pain at the bite site.51,54 This local prodrome is found more frequently in bat-exposed than in dog-exposed cases (70% vs 30%),51,55 which suggests a preferential sensory pathway. At this prodromal stage, prophylaxis with standard tissue-culture vaccine and rabies immunoglobulin has not been able to avert death.

Rabies virus can enter directly into nerves without previous replication in muscle or skin. This ability was confirmed by inoculation of rabies virus into the anterior chamber of the eye in rats, and in a mouse model by inoculation into the masseter muscle or the forelimb.56–58 A patient who had severe bite injury to the brachial plexus died within 5 days.52

Travel from the peripheral nerves to the CNS occurs at a fairly constant rate of 8–20 mm/day, and the time taken depends on the distance of the inoculation site from the CNS. Studies with the fixed challenge virus standard strain of rabies virus in cocultures of chick spinal cord and muscle showed that the neuromuscular junction is the major site of entry into neurons.59 Colocalisation of virus and endosome tracers within the nerve terminals, and progressive accumulation of virus and tracers in axons and nerve cell bodies, indicated retrograde transport of endocytosed virus from motor-nerve terminals.59 However, whether the endocytosis is mediated by the acetylcholine receptor, is a fluid-phase endocytosis, or is made possible by synaptic vesicle recycling is unknown.60,61 The nicotinic acetylcholine receptor is unlikely to be the only receptor that mediates viral entry into neurons, since it is not present on all types of neural terminals.
of neurons susceptible to rabies virus. The virus may also use carbohydrates, phospholipids, gangliosides, neural-cell adhesion molecule (CD56), and low-affinity nerve-growth-factor receptor (p75 neurotrophin receptor) to gain entry into the cells both in vitro and in vivo.62,63,64

Once the virus is in a neuronal cell, rapid amplification takes place. Virus disseminates via plasma-membrane budding and direct cell-to-cell transmission or by trans-synaptic propagation.65 The G protein is required for attachment to neuronal receptors as well as for trans-synaptic spread as shown by a study that used G–deficient rabies virus.66 The virus may travel by retrograde axonal transport via interaction between the microtubule dynein light chain (a cytoplasmic protein involved in the minus end movement of organelles along microtubules) and viral capsid P protein.67–69

**CNS infection**

After the virus reaches the CNS, rapid dissemination occurs. Nevertheless, rabies virus preferentially localises in the brainstem, thalamus, basal ganglia, and spinal cord irrespective of clinical presentation or bite site.70 Virus distribution alone may not explain the limbic symptom pattern or clinical diversity. The host and strain of virus do not explain clinical manifestations either, although rabies virus may travel by retrograde axonal transport as shown by a study that used G–deficient rabies virus.71 The virus may travel by retrograde axonal transport via interaction between the microtubule dynein light chain (a cytoplasmic protein involved in the minus end movement of organelles along microtubules) and viral capsid P protein.68–70

Pathophysiology

Weakness in paralytic rabies may be caused by peripheral-nerve dysfunction from a bystander effect of the immune attack against virus in the axons,67 or an autoimmune process against the peripheral nerve (because rabies-virus antibody was not detected in the CSF of Thai patients with paralytic rabies). HLA DR9 and DR17 were associated with susceptibility to encephalomyelitis and neuritis induced by Semple rabies vaccine in Thai patients.72 Further studies are required to elucidate whether genetic susceptibility has a role in determining whether an individual will develop paralytic rabies.

Cellular immunity to rabies virus may also accelerate the course and clinical manifestations.14 Patients with intact T-cell immunity to rabies virus, with high concentrations of serum interleukin-2 receptor and interleukin 6, die earlier and present with encephalitic rabies, whereas those lacking such responses survive longer and present with paralytic rabies.13,14,73 Findings in rodents are similar.14–16 Lack of T-cell response to virus in paralytic rabies is not explained by excessive cortisol production or by a panimmuno-suppressive process. Cortisol concentrations, although significantly higher than normal, were similar among patients with encephalitic rabies and others with paralytic rabies.15 Few patients with rabies of either type also showed cellular reactivity to myelin basic protein.14

In theory, rabies-virus infection of the CNS, particularly in the brainstem, leads to the production of cytokines and proinflammatory molecules, such as interleukins 1 α/β, 6, and 10, tumour necrosis factor α (TNFα), interferons, and nitric oxide, and to the secretion of chemokines (figure 4). These cytokines may modify the hippocampus and other limbic-system functions, including electrical cortical activity, the hypothalamo-pituitary-adrenal axis, and serotonin metabolism.74 However, this hypothesis may be inadequate to explain the terrifying picture of rabies. In encephalitic rabies, these locally-produced cytokines may further activate the p55 TNFα receptor, resulting in the recruitment of T and B cells.75 This action may lead to the promotion of immune recognition against rabies virus at “immune-privileged” sites, and provoke another amplification of the cytokine cascade, intensifying the limbic symptom pattern. Delayed mortality was observed in

---

**Figure 4. Hypothetical mechanisms in encephalitic rabies.** Production of proinflammatory molecules results from rabies-infected neuronal processes in the brainstem. These substances, in turn, lead to functional modification of the limbic system and stimulation of the hypothalamo-pituitary-adrenal (HPA) axis (red arrows). In encephalitic rabies, p55 TNFα receptors may also be activated. Rabies-virus antigen in the CNS is thus recognised. Subsequently, recruitment of immune cells and intensification of limbic symptoms and HPA stimulation follow (red arrows). Once Vβ8 T cells are stimulated by rabies-virus nucleocapsid antigens (blue arrows), these cytokine cascades are reamplified, exaggerating the disturbance of the limbic and sympathetic nervous systems.
mice deficient in the p55 TNFα receptor as a result of an increase in interferon γ and interleukin 10 and a reduction in inflammatory cells in the CNS.79 Furthermore, if Vß8 T cells are stimulated by rabies-virus nucleocapsid antigen,39 more cytokines are produced, thus exaggerating the functional disturbance in the limbic system even in the absence of virus in such structures. This process possibly explains the relative paucity of limbic dysfunction and absence of cellular immune activity to rabies virus in patients with the paralytic form.

Neither the amount of rabies virus in the CNS nor apoptosis seems to contribute significantly to pathogenesis. Rabies-virus antigen was readily demonstrable by immunofluorescence in the frontal area of a fully conscious paralysed patient who had quadriplegia and respiratory failure necessitating ventilatory support.14 The degree of modification of muscarinic acetylcholine-receptor function in the hippocampus of rabid dogs does not depend on the viral load.39 Pathological changes in neurons and inflammatory infiltrations in the brain do not consistently match the dramatic clinical picture, and apoptosis had been proposed as a principal cause of neuronal death; however, recent studies suggest otherwise.39 Apoptosis leads to depolymerisation of actin filaments, which in rabies would prevent transport of viral nucleocapsid protein and neuronal spread of virus. The extent of apoptosis correlates with the amount of expression of rabies-virus glycoprotein in infected neurons.35 Downregulation of glycoprotein expression in neuronal cells contributes to pathogenesis by preventing apoptosis.35 Apoptosis, therefore, should be one of the most important defence mechanisms against rabies-virus infection. Depletion of metabolic pools by excessive viral replication, which ultimately leads to downregulation of expression of the late host response gene and cell death, is a likely explanation of the virulence of rabies virus.

**Spread from the CNS**

Eventual centrifugal spread from the CNS along neural pathways to the heart, skin, and other organs, especially the salivary and serous glands of the tongue, is an important component to complete the infectious cycle.37 All major neural and non-neural organs, except for the blood, may contain significant amounts of virus. Organs of patients with an unexplained neurological disease, if transplanted, may transmit rabies.

**Diagnosis**

Establishment of a definitive clinical diagnosis of human rabies is difficult and requires the presence of cardinal signs in the encephalitic form. This requirement may not be helpful in areas without endemic canine rabies, where most cases have atypical presentations, associated with exposure to rabid bats or other wild animals.40 Furthermore, failure of diagnosis in more developed countries is probably related to the lack of a clear bite history, compounded by a lack of medical familiarity even with typical clinical features of the disease. Diagnosis on clinical grounds alone causes an imprecise assumption of low mortality from human rabies. Several patients with paralysis in Thailand had undergone plasma exchange because of a misdiagnosis of GBS. Examination of brain tissue obtained with a liver-biopsy needle aspiration via the transorbital approach should be required in all patients with encephalitis or paralysis who later progress to coma.36 Fluorescent examination of brain impressions for rabies-virus antigen is inexpensive, but it is extremely sensitive and reliable. This technique is available in most less developed countries. Physicians should be aware of the emergence of non-classic forms of rabies, which may reflect another reservoir or virus in that region.

**Differential diagnosis**

Differential diagnosis includes encephalitis caused by arboviruses such as Japanese, eastern equine, and West Nile viruses, and enterovirus-71 and Nipah-virus infections.36–39,95 Diffuse flaccid paralysis was found in 10% of patients with West Nile virus encephalitis, with no discernible ascending pattern of progression.39 Asymmetrical pure motor poliomyelitis-like weakness can be seen in patients with Japanese encephalitis.39 Myoclonus and other brainstem signs, such as bilateral ptosis and nystagmus (similar to those in patients infected by bat rabies virus) have been found in enterovirus-71 and Nipah-virus encephalitis.36–20

Acute hepatic porphyria with neuropsychiatric disturbances, and signs of autonomic dysfunction and ascending paralysis with bilateral facial weakness, may mimic rabies. Fluctuating consciousness is observed in both illnesses, but phobic and inspiratory spasms are seen only in rabies. Other disorders mimicking rabies include substance abuse, alcohol withdrawal or delirium tremens, and acute serotonin syndrome from taking serotonin-reuptake inhibitors.39 Tetanus resembles rabies only in the form of
reflex spasms. All patients with tetanus have a clear sensorium. Rabies patients do not have persistent rigidity or sustained contraction of axial musculature, such as the jaw, neck, back, and abdomen, as seen in tetanus. Spasms in rabies predominantly affect accessory respiratory muscles and the diaphragm, whereas in tetanus, spasms occur in axial muscles. Opisthotonos is extremely rare in rabies.

The axonal form of GBS, acute motor axonal neuropathy, shares many clinical features with paralytic rabies. Inspiratory spasms with abnormal behaviour may appear late in the clinical course and may be masked by generalised paralysis and superimposed metabolic disturbances that can occur in both disorders. Studies of nerve conduction do not differentiate paralytic rabies from GBS.

In some countries where rabies vaccines derived from nervous tissue are still widely used, neuroparalytic accidents must be included in the differential diagnosis. Such accidents occurred in as many as one in 400 patients treated with Semple vaccine and in a lower proportion of patients who received mouse brain vaccine. Neither phobic spasms, local prodromal symptoms, nor fluctuating consciousness are present in these postvaccination reactions.

**Antemortem diagnostic approach**

During life, routine laboratory studies are non-diagnostic. Hyponatraemia is present in most cases, owing to inadequate intake or the syndrome of inappropriate secretions of antidiuretic hormone. Hypernatraemia and polyuria are rare. The CSF may appear normal. Alternatively, CSF pleiocytosis in GBS-like patients, who have negative HIV serology, should alert the clinician, particularly when fever, hyponatraemia, and bladder disturbances occur early in the course.

Magnetic resonance imaging can be helpful in antemortem diagnosis of rabies. Both paralytic and encephalitic rabies patients had similar distribution of abnormal, ill-defined, mildly hypersignal T2 images involving the brainstem, hippocampi, hypothalami, deep and subcortical white matter, and deep and cortical grey matter with varying degree of severity depending on the stage of disease (figures 5 and 6). Gadolinium enhancement is clearly shown only in later stages (figure 7). Abnormalities in the putamen and globus pallidus, especially during the latter phase of disease, may be attributable to hypoxic insults. Although a seemingly similar involvement of thalamus and midbrain on magnetic resonance images can also be seen in patients with Japanese encephalitis, more prominent hypersignal T2 changes and foci of haemorrhages are observed in this disorder than in rabies. Hypersignal T2 changes at periventricular and deep white matter in rabies were not observed in Japanese encephalitis.

Specific serological tests may produce variable results. Rabies-virus antibody was detected in only 20% (six of 31)
of unvaccinated rabies patients tested within 1–26 days of disease onset.\textsuperscript{2,3} Antibody-positive serum samples can be obtained within 9 days after onset (within the first 3 days). However, analysis of 102 samples from 39 patients in the USA and 16 in France since 1960 showed that serum antibody generally developed if the patient survived longer than 8 days (six of 43 between days 1 and 8 compared with 34 of 59 from day 9). Antibody appeared in the CSF later (none of 19 between days 1 and 8 and ten of 28 on day 9).\textsuperscript{3,4} Nevertheless, out of 27 Thai patients, none had detectable rabies-virus antibody in the CSF.\textsuperscript{5,6}

Rabies-virus antigen in the neural innervation of hair follicles can be demonstrated by the fluorescent-antibody technique on frozen sections of the skin from the nape of the neck. Though sensitive, this technique may not be practicable in all settings, because of the requirement for a cryostat for preparation of ideal frozen tissue sections.\textsuperscript{4,5} Early studies suggested that the proportion of positive results should increase as the disease progressed,\textsuperscript{6} but the results of another study did not confirm this idea. Test sensitivity was 82% (five of six) when it was done within 4 days compared with 60% (six of ten) between days 5 and 8.\textsuperscript{7} Both corneal and salivary impressions for detection of rabies-virus antigen may be unreliable, because of differences in technique and interlaboratory variation in interpretation.

Brain biopsy, although not practicable, yields high sensitivity.\textsuperscript{8} Nevertheless, false-negative results may occur when biopsy at the frontotemporal region is done during the first days of illness. Occasional differential occurrence of viral antigen may be overcome by molecular detection, but only with much attention paid to strategies for proper primer design and extraordinary care taken to preclude cross-contamination.\textsuperscript{9,10}

In addition to CNS tissue, saliva, CSF, tears, skin biopsy samples, and urine may be sources for detection of rabies-virus RNA by reverse-transcription PCR or nucleic-acid sequence-based amplification.\textsuperscript{11,12,13,14,15} Serial samples should be tested, because not all are positive, owing to intermittent shedding of virus.

Management

Treatment is purely symptomatic, to lessen the degree of agitation and to comfort the patient and family. Fear of rabies is universal among health-care personnel, resulting in poor nursing care. Attending nurses and physicians who routinely care for patients with rabies may need preexposure vaccination, and other staff should receive postexposure treatment only if a true exposure occurs despite precautions. Past efforts to prevent fatal outcome have failed, with no spontaneous recoveries. A handful of survivors are known, essentially pre-exposure or postexposure treatment failures, with major sequelae.\textsuperscript{16,17} Attempted treatments include interferon and antiviral drugs such as ribavirin, vidarabine, aciclovir, and inosine pranobex, intrathecal and systemic high-dose administration of human rabies immunoglobulin, steroids, and antithymocyte globulin; none has been successful.\textsuperscript{18}

Acknowledgments

Our work has been supported by grants from the Thai Red Cross Society, the Thailand Research Fund, and the General Prayuth Charumuni, Cherdchai Wilailak, and the Phraya Athakrawesunthorn and Khunying Foundations.

Authors’ contributions

All authors contributed equally to all parts of the text.

Conflict of interest

We have no financial and personal relationships with other people or organisations that could inappropriately influence our work.

Role of the funding source

Sources of support for this work had no influence in the preparation of the review or in the decision to submit the paper for publication.

References

22 Tirawatnpong S, Hemachudha T, Manunathit S,
Rabies mechanisms and diagnostic challenges

Review


