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Mini-Review—The Rabies Virus

Pathophysiology of human paralytic rabies

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Furious rabies is a well-recognized clinical disorder in humans but the paralytic form is not as easily identified. The mechanisms responsible for the weakness and longer survival periods are not clear. Several hypotheses have been proposed, including rabies virus variants associated with a particular vector, location of wounds, incubation period, influence of prior rabies vaccination, and virus localization in the central nervous system (CNS). However, none of these have been substantiated. Regarding molecular analyses of rabies viruses isolated from both furious and paralytic rabies patients, only minor genetic variations with no specific patterns in glyco- (G), phospho- (P), and nucleoprotein (N) sequences have been identified and arginine 333 in G protein was present in all samples. Regional distribution of rabies virus antigen in rabies patients whose survival periods were 7 days or less and magnetic resonance imaging (MRI) of the CNS indicated brainstem and spinal cord as predilection sites regardless of clinical presentations. There are clinical, electrophysiological, and pathological indications that peripheral nerve dysfunction is responsible for weakness in paralytic rabies whereas in furious rabies, even in the absence of clinical weakness, abundant denervation potentials with normal sensory nerve conduction studies and proximal motor latencies suggest anterior horn cell dysfunction. The lack of cellular immunity to rabies virus antigen accompanied by an absence of cerebrospinal fluid (CSF) rabies neutralizing antibody in most paralytic rabies patients may argue against role of an immune response against rabies virus–positive axons. Aberrant immune responses to peripheral nerve antigen, in particular those mediated by one or more cellular-dependent mechanisms, may be involved as is supported by the absence of putative anti-ganglioside antibodies commonly found in immune-mediated peripheral nerve diseases. Longer survival period in paralytic rabies may possibly be related to currently unidentified mechanism(s) on neuronal gene expression, required for virus transcription/replication and for maintaining neuronal survival. *Journal of NeuroVirology* (2005) **11,** 93–100.

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Introduction

Furious rabies has been recorded since antiquity (Rupprecht and Hemachudha, 2004) but the paralytic form of the disease was not recognized until much later. It was initially recorded in 1887 (Gamaleia, 1887) but not widely identified until decades later (Chopra *et al*, 1980; Pawan, 1939). Paralytic rabies continues to be confused with Guillain-Barré syndrome (GBS) and related disorders, treatable autoimmune diseases of peripheral nerves. Misdiagnoses of rabies has led to human-to-human transmission

through corneal, liver, and kidney transplants from donors who were thought to have GBS or stroke (Jackson, 2002; Lanska, 1992; *MMWR*, 2004). Many rabies patients misdiagnosed as GBS have undergone plasma exchange (Hemachudha *et al*, 2002).

Survival time in paralytic rabies is longer than in furious rabies (Hemachudha *et al*, 2002). We have also demonstrated that dysfunction of peripheral nerves, not anterior horn cells, is responsible for weakness in paralytic rabies (Mitrabhakdi *et al*, 2004).

In order to improve the diagnosis of human rabies, there is a need to better recognize paralytic rabies patients. This article summarizes the distinct clinical features associated with paralytic rabies as compared to GBS and furious rabies. Data on the electrophysiological and pathological features and magnetic resonance imaging (MRI) findings are also reviewed. In addition, we present hypotheses regarding the pathophysiologic mechanisms in paralytic rabies patients.

Clinical features

Furious and paralytic rabies

Clinical data from 115 Thai rabies patients (furious 80, paralytic 35) were examined and compiled from our published reports between 1988 and 2004. These data revealed longer survival periods in the paralytic rabies group (11 days versus 5.7 days in furious group). Cardinal features of furious rabies, fluctuating consciousness, hydro- or aerophobia and inspiratory spasms, signs of autonomic dysfunction, were seen in all Thai furious rabies patients. In noncanine rabies endemic areas, such as in North America, where bats are the principle vector of rabies, clinical expression may be variable (Hemachudha and Phuapradit, 1997).

Only one or two classical signs of rabies, or even none, may be seen during the whole clinical course in paralytic rabies. Consciousness was preserved until the preterminal phase. Phobic spasms were reported in only half of our confirmed paralytic rabies patients (Hemachudha and Rupprecht, 2004). Weakness was the initial manifestation in paralytic rabies, whereas this was noted only when furious rabies patient approached coma.

Paralytic rabies and Guillain-Barre syndrome

There are some unique clinical features associated with GBS and paralytic rabies, but some can overlap. This to the extent that they may be indistinguishable clinically (Hemachudha, 1989; Kissel *et al*, 2001; Mitrabhakdi *et al*, 2004) (Table 1).

All three main subtypes of GBS, in which weakness is predominant, result from an immune-mediated process directed against Schwann cells and myelin or axolemma of motor and sensory fibers (Griffin *et al*, 1996; Hafer-Macko *et al*, 1996a, 1996b; McKhann *et al*, 1993) (Table 1).

Table 1 Clinical features of paralytic rabies and GBS

Paralytic rabies	Fever, local prodrome in 1/3*, phobic spasms in 1/2
	Rare distal paresthesias, percussion myoedema
	Ascending weakness, may start at bitten limb
	Average survival period = 11 days (versus 6 days in furious rabies)
AIDP**	2/3 have antecedent viral or bacterial infections
	Symptoms begin with pain and paresthesias in 1/2
	Ascending weakness in 90%, descending weakness initially at the arms in 10%, 80% recovery in 6 months
AMAN***	Commonly preceded by diarrhea from *C. Jejuni*
	Abrupt onset of weakness, quadriplegia, respiratory failure
	Recovery pattern similar to or better than AIDP
AMSAN****	Commonly preceded by diarrhea from *C. Jejuni*
	Minimal sensory symptoms
	Abrupt onset of weakness, quadriplegia, respiratory failure, may have ophthalmoparesis
	Longer recovery period as compared to AIDP and AMAN

*In dog-related cases; 2/3 in bat-related cases.
**AIDP = acute inflammatory demyelinating polyradiculoneuropathy.
***AMAN = acute motor axonal neuropathy.
****AMSAN = acute sensory axonal neuropathy.

Similarities with GBS and paralytic rabies are not seen in paralysis associated with other viral infections such as flaviviruses, poliovirus, and West Nile virus where anterior horn cell involvement has been documented by electrophysiologic and magnetic resonance studies (Gorson and Ropper, 2001; Leis *et al*, 2002; Li *et al*, 2003; Solomon *et al*, 1998).

Clinical similarities of GBS and paralytic rabies raise questions whether both share the same neuroanatomical involvement and whether mechanisms responsible for weakness in paralytic rabies are immunologic in nature as has been reported for GBS in association with *Campylobacter jejuni*, *Mycoplasma pneumoniae*, cytomegalovirus, and Epstein-Barr virus (Ogawara *et al*, 2000).

Pathophysiology of paralytic rabies

Neuroanatomical base for weakness

Symptoms and signs in paralytic and furious rabies are indicative of derangement of spinal cord (anterior horn cell) or peripheral nerve in the former and cerebral functions in the latter. Although MRI is useful in aiding diagnosis, MRI fails to explain the clinical diversity in human rabies (Laothamatas *et al*, 2003). This is also true in the case of distribution of rabies virus antigen and inflammatory reactions in the CNS (Tirawatnpong *et al*, 1989). Evidence supporting peripheral nerve dysfunction is based on electrophysiologic studies, the result of which is in accord with peripheral nerve pathology.

MRI in human rabies: MRI clearly demonstrated anterior horn cell involvement in paralytic patients

associated with flaviviruses, poliovirus, and West Nile virus (Gorson and Ropper, 2001; Leis *et al*, 2002, 2003; Li *et al*, 2003; Sejvar *et al*, 2003a, 2003b; Solomon *et al*, 1998, 2000a, 2000b). Asymmetric flaccid paralysis with or without signs of meningoencephalitis as well as reversible paraparesis or monoparesis can be seen in association with West Nile virus infection (Leis *et al*, 2003).

In human rabies of both forms, spinal cord gray matter and anterior horn cell were involved in axial gradient-echo T2-weighted images; however, lateral and posterior columns were also affected (Laothamatas *et al*, 2003). Furthermore, MRI findings of the brain were similar in five rabies patients (two furious and three paralytic) and demonstrated as ill-defined, mild hyperintensity changes in the brain stem, hippocampi, hypothalami, deep and subcortical white matter, and deep and cortical gray matter on T2-weighted images (Laothamatas *et al*, 2003). Such findings were evident as early as day 3 after onset and even when consciousness remained intact. Only when the patients became comatose that contrast-enhanced lesions could be demonstrated in brainstem, hypothalami, and spinal nerve roots.

Neither the distribution of rabies virus antigen nor inflammation can explain MRI abnormalities and clinical symptomatology. Of seven patients studied, four (three furious and one paralytic) who had survival times of 7 days or less had a greater amount of antigen-positive neurons in brain stem and spinal cord by avidin-biotin immunoperoxidase staining (Tirawatnpong *et al*, 1989). Hippocampi and hypothalami contained a very minimal amount of rabies antigen. It was not until day 8 after clinical onset that rabies virus antigen disseminated throughout the whole neuraxis, including deep and cortical gray matter. Inflammation was scant in all cases in relation to the amount of viral antigen and survival time. It was not limited to spinal cord in paralytic cases. Inflammation, when present, was usually found in the brain stem and/or spinal cord.

It is also intriguing regarding the pathological basis of MRI changes in the white matter (Laothamatas *et al*, 2003). Extensive demyelination has been reported in one furious rabies patient (Nelson and Berry, 1993), but demyelination in the brain was not observed in another histopathologic series (Chopra *et al*, 1980; Tangchai *et al*, 1970; Tirawatnpong *et al*, 1989). Whether this is caused by alteration of actin-based cytoskeleton mediated by rabies virus nucleocapsid remains to be determined (Ceccaldi *et al*, 1997).

Hyperintense lesions on T2-weighted MRI scans are related primarily to increased water content and thus cannot distinguish between inflammation, edema of vasogenic or cytotoxic origin, demyelination, wallerian degeneration, and axonal loss as well as disruption of cellular or blood brain/nerve barrier integrity (Chard *et al*, 2002; Zivadinov and Bakshi, 2004). Therefore, MRI may not show a reliable correlation with clinical disablitiy. In a disease with a high degree of variability of clinical signs and symptoms such as rabies, newer techniques are required to elucidate mechanisms underlying tissue damage.

Electrophysiologic features in paralytic rabies: Electrophysiologic studies showed evidence of peripheral nerve dysfunction in all three paralytic rabies patients with findings indistinguishable from demyelinating and axonal GBS variants (Mitrabhakdi *et al*, 2004).

Dysfunction of peripheral nerve was suggested by findings of multifocal demyelination along with length-dependent sensory neuropathy in one patient; severe reduction in conduction velocities and marked prolongation of distal latencies in another patient; and progressive loss of motor and sensory amplitudes without accompanied denervation potentials in the third patient who also had early abnormalities in late response indicative of proximal nerve segment involvement during sequential examinations on days 3, 4, 6, and 8 after clinical onset.

Local neuropathic pain is also likely to be due to dorsal root ganglionopathy based on the evidence of absence or progressive decline in sensory nerve action potential amplitudes in the bitten segment.

As opposed to the electrodiagnostic findings in paralytic rabies, the sensory and motor nerve conduction studies, including late responses in three furious patients, were normal. Abundant denervation potentials were evident primarily in the bitten limb even before clinical weakness appeared. This suggests an acute motor fiber loss, probably at the anterior horn cell level. Recent studies also showed that rabies virus–infected rat spinal cord motoneurons resist cytolysis, and apoptotic process is delayed in these neurons as compared to hippocampus cells (Guigoni and Coulon, 2002). Hence, all of these may suggest peripheral nerve dysfunction as being responsible for weakness in paralytic rabies.

Pathology: Histopathological study performed on 11 paralytic rabies patients suggested peripheral nerve demyelination as the prime change (Chopra *et al*, 1980). Mild-to-moderate loss of myelinated nerve fibres was reported in 11 of 17 nerves examined; segmental demyelination and remyelination in 16 teased nerve preparations; axonal loss of a variable degree was present in 4 cases; and wallerian-like degeneration in teased single fibres was noted in 6 nerves (Chopra *et al*, 1980). In 9 nerves, the primary abnormality was segmental demyelination and remyelination or myelinated nerve fiber loss, either singly or in combination. In none of these cases was wallerian-like degeneration seen as the only pathological feature. All spinal nerve studies showed evidence of wallerian-like degeneration as well as segmental demyelination (Chopra *et al*, 1980). Such

Table 2 Pathological features of paralytic rabies and GBS

Paralytic rabies	1. Primarily segmental demyelination and remyelination, occasionally accompanied by wallerian-like degeneration 2. T cell–mediated immune attack and/or antibody-mediated complement attack at rabies virus positive axon (or peripheral nerve antigen?) 3. Marked inflammatory infiltration of spinal nerve roots by T cell, dorsal root ganglionitis in segment of sensory prodrome
AIDP	1. Demyelination of nerve roots and peripheral nerve fibers 2. Antibody-mediated complement attack at Schwann cells, plasmalemma, especially in nerve roots followed by macrophage-mediated demyelination 3. Cellular infiltrations not consistent. When present, found predominantly in nerve roots 4. Axonal degeneration in severe case
AMAN	1. Axonal degeneration affecting large myelinated fibers of ventral roots 2. Antibody-mediated complement attack at axonal plasmalemma and macrophage recruitment to nodal region 3. Lack of significant lymphocytic infiltration 4. Most axons recover from injury without undergoing wallerian-like degeneration
AMSAN	1. Severe axonal degeneration of myelinated and unmyelinated nerve fibers of nerve roots, with subsequent extension to peripheral nerves 2. Antibody-mediated complement attack at axonal plasmalemma and macrophages recruitment to the nodal region 3. Lack of significant lymphocytic infiltration 4. Extensive wallerian-like degeneration in nerve roots Peripheral nerves are involved later

demyelination was absent in the case of furious rabies (Tangchai and Vejjajiva, 1971).

Our recent histopathological examination of two paralytic and one furious rabies patients agrees with previous reports (Mitrabhakdi *et al*, 2004) (Table 2). All of them had local neuropathic symptoms. In both paralytic cases, moderate to severe degree of lymphocytic infiltrations, mainly of CD3-positive T cells, was evident in dorsal and spinal nerve roots. The degree of inflammation appeared to be greater at the level of bitten segment. Inflammation of less intense degree was also seen in spinal cord gray matter. Anterior horn cells appeared intact in one and depleted in another but no central chromatolysis was observed in the remaining cells. Only mild inflammation of the spinal nerve roots at all levels was observed in furious rabies patient who had a bite at right ankle. Moderate mononuclear inflammatory cell infiltrates were present in the spinal gray matter of thoracic and lumbar levels and, to a lesser extent, in the cervical cord. Some of the anterior horn cells demonstrated central chromatolysis. Dorsal root ganglionitits was found in all cases.

Inflammation and demyelination of the spinal nerve roots and peripheral nerve, therefore, are characteristic findings in paralytic rabies (Chopra *et al*, 1980; Mitrabhakdi *et al*, 2004). Although inflammation was also evident in spinal cords of these patients, this may not be a constant finding. As mentioned previously, spinal cord inflammation was scant in all four furious and in three paralytic rabies patients in relation to viral antigen and survival time. It was also not limited to the spinal cord in paralytic cases (Tirawatnpong *et al*, 1989).

Nevertheless, it is not known when inflammation and peripheral nerve demyelination take place. If these occur during centrifugal spread of the virus transport, functional derangement of the peripheral nerve as evidenced by electrodiagnostic test may not be necessarily explained by such pathology.

Immunologic mechanisms as critical factors in determining survival period and clinical manifestations in human rabies

Immunologic parameters in human furious and paralytic rabies: The term "early death" phenomenon has been coined to emphasize the immune role in accelerating deaths in rabies-infected animals (Blancou *et al*, 1980; Prabhakar and Nathanson, 1981). Immunosuppressed animals show a delay in death (Ceccaldi *et al*, 1996; Iwasaki *et al*, 1977; Smith *et al*, 1982; Tignor *et al*, 1974). Studies in animals with accelerated death indicate that paralysis is a CD4 and CD8 T cell–dependent immunopathologic phenomemon. Foot pad inoculation of a temperature-sensitive variant of the CVS or with the Evelyn-Rokitnicky-Abelseth strain induced paralysis with severe necrosis or degeneration of myelinated motor neurons of the spinal cord in immunocompetent mice (Iwasaki *et al*, 1977; Weiland *et al*, 1992). Street rabies virus–infected T lymphocyte–deficient (nude) mice developed hind limb paralysis after receiving passive transfer of spleen cells (with T cells) from normal immunocompetent mice (Sugamata *et al*, 1992). Perivascular infiltrates included CD8+ and CD4+ T lymphocytes and Mac-1+ macrophage microglial cells.

In human rabies, six of nine furious rabies patients had T-cell immunity to rabies virus based on *in vitro* lymphocyte stimulation technique, whereas none of seven paralytic patients had such response (Hemachudha, 1994; Hemachudha *et al*, 1993, 1988). In another study, more furious patients had raised soluble interleukin-2 (IL-2) receptor (sIL2R) (12/22 versus 1/6 paralytic) and IL-6 levels (5/22 versus 0/6), whereas sCD8 levels were rarely elevated in both groups (Hemachudha *et al*, 1993). Lack of T-cell responses to rabies virus in paralytic rabies is not explained by excessive cortisol production or by a pan-immunosuppressive process. Although serum cortisol levels were elevated in human rabies patients, their levels were comparable among both forms (Hemachudha, 1994). Antigen-specific cell-mediated immune response suppression in mice infected with pathogenic lyssaviruses has

been reported (Perrin *et al*, 1996). There were no differences in total T-cell and T suppressor/cytotoxic–cell numbers in four furious and three paralytic patients, although B-cell numbers were diminished exclusively in all three paralytic cases (Sriwanthana *et al*, 1989). Cellular reactivity against antigens other than rabies, such as myelin basic protein, could still be demonstrated in some of furious and paralytic rabies patients (Hemachudha *et al*, 1988).

Although there is a general agreement that immunopathologic mechanisms may accelerate death and influence the clinical outcome in both human rabies and animal models, specific virus variant itself may be entirely responsible for the outcome and any accompanying immunological findings could be merely epiphenomenon. Rabies glycoprotein is crucial for neutralizing antibody production and initiation of cellular immunity response. Differences in glycoprotein (G) may affect G protein–receptor interactions, nicotinic acetylcholine receptor at bite site, P75 neurotrophin receptor, and glycolipid or ganglioside central nervous system (CNS) receptors. Minor variations of the G protein, such as an amino acid substitution of arginine at position 333, may affect neuroinvasiveness by the use of different neuronal pathways (Wunner, 2002). Pathogenicity of different rabies virus variants inversely correlates with apoptosis and rabies virus glycoprotein expression based on study in infected primary neuron cultures (Morimoto *et al*, 1999). Modifying the dynein light chain binding site to rabies virus capsid P protein can reduce the efficiency of the peripheral spread of certain rabies virus (Mebatsion, 2001).

Comparison of a 1-432-, a 1575-, and a 894-nucleotide region from the rabies virus N, G, and P protein genes of samples obtained from two furious and two paralytic human patients associated with canine rabies virus of genotype 1 showed only minor nucleotide differences (Hemachudha *et al*, 2003b). Deduced amino acid patterns of N protein were identical among both human and canine samples that belonged to the same geographic origin, regardless of clinical forms. All differences in the amino acid of G protein were found outside the ectodomain, in the signal peptide and transmembrane and endodomains. None were in an interactive region with receptors known responsible for virus pathogenicity, nor did they lie in an immunodominant G domain. Moreover, a single rabid dog transmitted furious rabies to one patient and paralytic rabies in another (Hemachudha *et al*, 1988).

Both the involvement of peripheral nerves in paralytic rabies and the unexplained aggression with extreme excitability in furious rabies, despite a similar virus distribution in the CNS and nearly identical MRI patterns in the brain, argue against the existence of specific variants, and instead, suggest a participation of host factors. The degree of functional impairment of the muscarinic acetylcholine receptor in the brains of rabid dogs does not correlate with the virus distribution and virus load (Dumrongphol *et al*, 1996).

In human rabies, proinflammatory cytokines might also affect, directly or indirectly, the levels of neurotrophins, growth factors, neurotransmitters, and neurotoxins in the brain, via the activation of glia, neurons, and vascular and immune cells (Hemachudha *et al*, 2002; Tomonaga, 2004). It is not known to what extent that the initiation of immune response and amplification of cytokine cascade in rabies-infected brain (Hemachudha *et al*, 2002) can influence rabies virus modulation of host gene expression (Prosniak *et al*, 2001). Differences in the host neuronal gene expression patterns may be important in virus replication and spread in the CNS as well as neuronal survival (Prosniak *et al*, 2003). Perturbation of such cellular factors could also induce functional loss and/or abnormal activation of infected neural cells, leading to broad incoordination of the neural system (Tomonaga, 2004).

Hypothetical mechanisms in human paralytic rabies: Mechanisms involved in nerve injury could be mediated by rabies neutralizing antibody against rabies virus in axons. Neutralizing antibody was present as early as 3 days after onset of nonspecific symptoms (Kasempimolporn *et al*, 1991). Deposition of immunoglobulin G (IgG) and complement on rabies virus–positive axons was evident in a Chinese paralytic rabies patient (Sheikh *et al*, 1998). Viral protein and wallerian-like degeneration were found to be more abundant in the ventral than in dorsal nerve roots. Our recent case with furious rabies developed weakness of facial, limb, and neck flexor muscles 36 h after receiving intravenous human rabies immune globulin (Hemachudha *et al*, 2003a). However, there may be more than one mechanism involved because cerebrospinal (CSF) rabies neutralizing antibodies could not be demonstrated in this case as well as in another 30 rabies patients, 14 of whom were cases of paralytic rabies (Hemachudha and Mitrabhakdi, 2000; Laothamatas *et al*, 2003).

Auto-antibody against peripheral nerve antigen may be another mechanism. Vivid enhancement of the ventral and dorsal nerve roots could be demonstrated in two cases of paralytic rabies (Laothamatas *et al*, 2003). Such enhanced nerve roots can also be found in other conditions and in almost all of classical GBS patients (Gorson *et al*, 1996).

Molecular mimicry has been accepted for classical GBS and its variants. There appears to be a link between anti-glycolipid antibodies and many pathogens (Willison and Yuki, 2002). These autoantibodies were found associated with GBS and its variants and Bickerstaff's encephalitis (Odaka *et al*, 2003; Susuki *et al*, 2004; Willison and Yuki, 2002). None of our three furious and three paralytic rabies patients had anti-GM1, -GD1a, -GalNAc-GD1a, -GD1b, -GT1a, and -GQ1b ganglioside antibodies (Mitrabhakdi *et al*, 2004). Nevertheless, this does

not exclude the existence of other pathogenic autoantibodies.

It may be possible that antibody production in paralytic rabies may be inefficient. We have shown that some paralytic rabies patients had diminished circulating B cells and IL-6 levels (Hemachudha *et al*, 1993; Sriwanthana *et al*, 1989). Fewer paralytic rabies patients had serum rabies neutralizing antibody (Hemachudha and Phuapradit, 1997). Rabies patients with cellular reactivity to MBP did not have anti-MBP antibody (Hemachudha *et al*, 1988).

Other proposed factor for inducing weakness includes initiation of cellular-dependent mechanisms. Pathological examination of the peripheral nerve and spinal nerve roots indicated a more severe degree of inflammation in paralytic than in furious rabies patients (Chopra *et al*, 1980; Mitrabhakdi *et al*, 2004). Cellular infiltrates were characterized as T cells. Whether they are directed against rabies virus or peripheral nerve antigen is not known. Rabies virus, in the form of uncoated nucleocapsids or nascent ribonucleoprotein, migrates along peripheral nerve via fast retrograde axonal transport (Mebatsion, 2001; Murphy, 1977; Wunner, 2002). Rabies phosphoprotein interacts with LC8 component of dynein light chain in the transportation process (Mebatsion, 2001). The whole rabies virion, or only a subviral fragment containing glycoprotein (G) molecule, may also be carried by means of vesicular cargo using attachment between rabies G protein and p75NTR (Mazarakis *et al*, 2001; Tuffereau *et al*, 2001). Peripheral administration of rabies G-pseudotyped equine infectious anemia virus vectors to the rat gastrocnemius muscle leads to gene transfer in motoneurons of lumbar spinal cord (Mazarakis *et al*, 2001). Therefore, peripheral nerve containing noninfectious rabies virus, or just a subfragment, can be attacked by immune cells. Persistence of neuroadapted Sindbis virus antigen promotes progressive CNS neuronal damage and demyelination despite clearance of infectious virus. This is mediated by CD4 T cells and macrophage/microglia cells (Kimura and Griffin, 2003). Lack of specific cellular immune response to rabies virus is found in most paralytic rabies patients (Hemachudha *et al*, 1988). Hence, nerve cell–derived antigen may be a primary target in paralytic rabies. A strict homology between self- (peripheral nerve antigen) and foreign (rabies virus) antigens may not be necessary for cross recognition according to the concept of degenerate T-cell receptors (Gran *et al*, 1999).

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