SYLLABUS

TC09: Infection 2

Sunday, November 13, 2011 09:00 - 12:30 Hall L

Marrakesh, Morocco, November 12-17, 2011

XXth WORLD CONGRESS OF NEUROLOGY

XXth WCN 2011 MARRAKESH World Congress of Neurology

WFN

SMN SOCIETE MAROCAINE DE NEUROLOGIE

WCN Education Program

Sunday, 13 November, 2011

09:00-12:30

INFECTION 2

Chairperson: **Alan C. Jackson**, *Canada*

HCV NEUROTROPISM AND NEUROVIRULENCE
Christopher Power, *Canada*

NEUROLOGICAL MANIFSTATIONS OF FALCIPARUM MALARIA
Charles Newton, *Kenya*

EMERGING ENCEPHALITIS
Alan C. Jackson, *Canada*

10:30-11:00 *Coffee Break*

Emerging Encephalitis

Thiravat Hemachudha, MD, FACP
Department of Medicine (Neurology)
and WHO collaborating center for
research and training on viral zoonoses
Chulalongkorn University
Bangkok, Thailand.

Goal

The participants will:

- Recognize factors influencing emergence of encephalitis outbreaks
- Understand the environmental/climate changes and human behavior with respect to zoonotic and vector borne diseases.
- Be prepared for potential outbreaks in advance

Organization

- **Definition of emerging disease/encephalitis**
  Discuss emerging or expanding pathogens or those that have preexisted but expand in geographic range, move from one host species to another with increasing impact or severity
- **Importance of zoonotic/vector borne diseases**
  Of more than 1400 pathogens in humans, two-thirds are zoonotic/vector borne diseases. Thirteen percent can be categorized as emerging infectious diseases, among which 37% are RNA viruses. One half are RNA viruses that cause encephalitis.

Organization

- **Factors influencing emergence of encephalitis outbreaks**

  emergence of new agents or entry of viruses into new hosts or environments. In arboviral /zoonotic encephalitides, mechanisms influencing transmission include seasonal preference, abundance of vector/reservoir (and amplifying host), host factors (in terms of immunity, cross-protective immunity and diversity) and those contributed by humans (such as, urbanization, travel, animal trade, ignorance).

  Extreme weather events may also create conditions conductive to disease outbreaks.

  Factors that promote closer contact between human/domestic animal and (wild) animal/insect as well as movement of vector/reservoir into new geographical regions. Arbovirus evolution *in vivo* can also facilitate host range changes and lead to epidemics, although this is constrained by alternating infection of disparate hosts.

  Unexpected crossings of species barrier is an example of microbial success in intruding across the lines of defense. This was evidenced by transmission of Nipah virus from pteropid bats to pigs and man.

  Pure negligence of humans as prime factor in causing encephalitis outbreaks can be seen in the case of rabies where there is no commitment from policy makers, public ignorance of dog vaccination/population control.

  Microbial adaptation can lead to new clinical presentation such as with enterovirus -71 associated rhombencephalitis. Such adaptation and environmental changes also promote expansion of the vector host species range.

Organization

- **Properties of newly emerging encephalitis pathogens**

  a) effective maintenance system (reservoir, amplifying host, and transmitting vector) which is widely present in a large geographical location.

  b) able to escape notice by absence of CSF pleocytosis and only cause minor abnormalities on neuroimaging, confusing neurologists to misdiagnose them as metabolic disorders or intoxication.

  c) diverse manifestations neurologically (one form as myelitis and another as encephalitis or meningitis) or even as different syndromes, such as gastrointestinal symptoms or pneumonia.

  d) Rapid spreading with high infection rate and/or high morbidity/mortality are other key factors in such a new pathogen becoming an effective public health threat.

How to become an effective emerging CNS pathogen?

- ***Severe impact***
  national security
  rapidly spread
  high morbid/mortality
- ***Maintenance system***
  reservoir amplifying
  transmitting vector
- ***Able to Disguise***
  different manifestations (in such organ system or in other organ)
- ***Escape notice***
  normal CSF/ neuroimaging

Examples of pathogens causing severe outbreaks.

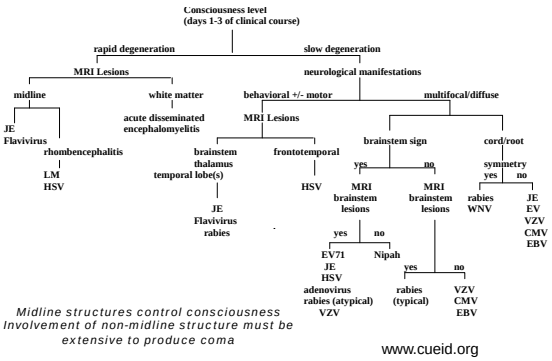
- Important emerging encephalitides will be briefly discussed focusing on origin, neurological manifestations, their unique characteristics and numbers of outbreaks.
- These include arboviruses (West Nile, Tick borne, Japanese encephalitis), paramyxovirus (Nipah), enterovirus (EV-71), Vesiculovirus (Chandipura virus) and dengue virus (with high number of infected cases but low prevalence of encephalitis), etc.
- Diagnosis relies on information derived from history taking, neuroimaging patterns and epidemiological data in the region. It needs to be confirmed by specific laboratory studies which are now increasingly available.

When should neuroimaging results be called "negative"?

- Findings in MRI depend on stage (timing when performed) and etiology of the disease. Some abnormal signals may be caused by the etiological agent or by a complication such as localized edema or hemorrhage, or an indirect effect such as hypoxia and bleeding from a coagulation defect. Diffusion weighted image and apparent diffusion coefficient techniques should be applied to detect early or micro-structural damage and to define edematous processes. Diffusion tensor imaging, mean diffusivities and fractional anisotropy, is useful in making diagnosis of encephalitides.

Algorithm in diagnosing encephalitis

- Combining data on rapidity of the disease course to coma, anatomical structural involvement according to clinical examination, findings on MRI, and whether there is any discrepancy between neurological signs and MRI lesions, algorithms can be constructed. These may aid in determining which pathogen group might be responsible.



Rupprecht, Hanlon, Hemachudha. Lancet Infect Dis 2002
Hemachudha, Rupprecht. Principle of Neurological Infectious Disease. McGraw Hill 2004.

Preparatory measures

- Preparation for potential outbreaks can be done by monitoring epidemiology in surrounding regions and significant new population movements. Knowledge of clinical/neurological manifestations, their neuroimaging patterns, age-group patterns of patients, duration of illness, morbidity/mortality rates, rapidity of spread, reservoirs and transmitting vectors are of utmost importance. This knowledge can alert health workers and aid early coping with a potential outbreak.

Surveillance of existing pathogens/vectors/amplifying hosts/immune status of residents

- Pro-active surveillance may forecast whether a disease which is endemic in nearby regions can expand and cause a new outbreak. Having such a program in place, will serve warning, and rapid response. An abundance of vector-reservoir species with high infective rates should alarm neurologist to look for new cases close to home. Atypical clinical presentations, once there is an outbreak, should be suspected as variants of the same disease until proven otherwise. Disease with available vaccines provide an added advantage. Vaccination programs can be started early when the outbreak is recognized.

Policies

- Neurologists must not practice in isolation. There is no satisfaction in making presumptive unconfirmed clinical diagnoses. A correct diagnosis is only made by detailed history-taking and examination as well as appropriate laboratory testing. The data must become part of the analysis of outbreaks so that public health authorities can plan managements.
- Attention should be paid on which specimens and at what time after the development of disease or neurological onset these specimens are best collected. Which kind of testing; microscopy, antibody-, antigen-assay, or nucleic acid amplification technique, yield reliable result and with which biological sample, and at what time during the disease course do these tests provide high sensitivity. Specificity of a particular test should also be known.
- If the disease is associated with animals or insects, only one identified case suffices as a signal that further casualties are likely.
- Interpretation of MRI findings in patients with encephalitis is always problematic. Having access to specialists in this field to whom MRI data can be uploaded by hi-speed internet is desirable. Contacts should be established in advance.
- Every outbreak should also be considered as a research opportunity for newer and better diagnostic tools or for improvements in existing tools and their interpretation (example imaging and molecular diagnosis).
- The management plan of an outbreak should be a joint project between neurologists and infectious disease specialists in order to have access to the latest laboratory diagnostics and to avoid contamination of public places and hospitals. This is especially important when human-human transmission has been documented
- A localized outbreak of zoonogic disease has to be investigated by physicians as well as veterinary scientists and wildlife experts. Identification of the origin and vector (if newly introduced to region) and sequencing of the virus may help formulate future prevention plans.

Expectations

- Enthusiasm of neurologists to work and join forces with veterinary scientists and wildlife experts as well as public health personnel

Requirements : Suggested readings:

- Nature Medicine. 2004; 10 (suppl). Review on emerging infectious diseases. War between humans and microbes.
- Journal of Neurovirology 2005; 11. Review on emerging encephalitis.
- Johnson RT, Power C.Emerging issues in neurovirology: new viruses, diagnostic tools, and therapeutics. Neurol Clin. 2008;26:855-64.
- Davis LE, Beckham JD, Tyler KL. North American encephalitic arboviruses.Neurol Clin. 2008;26:727-57.
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- Mansfield KL, Johnson N, Phipps LP, Stephenson JR, Fooks AR, Solomon T.Tick-borne Encephalitis Virus - a Review of an Emerging Zoonosis. J Gen Virol. 2009 May 6. [Epub ahead of print].
- Tobias E. Erlanger, Svenja Weiss, Jennifer Keiser, Jürg Utzinger, and Karin Wiedenmayer. Past, Present, and Future of Japanese Encephalitis.Emerging Infectious Diseases. www.cdc.gov/eid Vol. 15, No. 1, January 2009
- Tan CT, Chua KB. Nipah virus encephalitis. Curr Infect Dis Rep **2008**;10: 315-20.
- Rao BL, Basu A, Wairagkar NS, Gore MM, Arankalle VA, Thakare JP, Jadi RS, Rao KA, Mishra AC. A large outbreak of acute encephalitis with high fatality rate in children in Andhra Pradesh, India, in 2003, associated with Chandipura virus. Lancet 2004; 364: 869–74
- Tandale BV, Tikute SS, Arankalle VA, Satha PS, Joshi MV, Ranadive SN,Kanojia PC, Eshwaracharya D, Sumariwamy M, Mishra AC.Chandipura virus: a major cause of acute encephalitis in children in North Telangana, Andhra Pradesh, India. J Med Virol. 2008;80:118-24
- Tyler KL. Emerging viral infections of the central nervous system. Part 1. Arch Neurol 2009; 66: 939-48.
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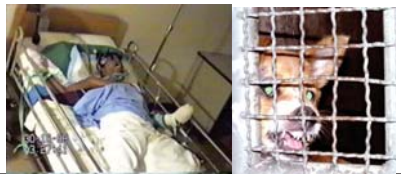
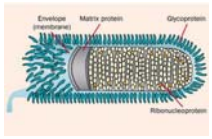
- Narasimha Rao S, Wairagkar NS, Murali Mohan V, Khetan M, Somarathi S.BrainStem encephalitis associated with chandipura in Andhra Pradesh outbreak. J Trop Pediatr. 2008; 54: 25-30. Epub 2007 Sep 28.
- Hemachudha T, Wacharapluesadee S, Laothamatas J, Wilde H . Rabies.Curr Neurol Neurosci Rep. 2006; 6: 460-8.
- Laothamatas J, Wacharapluesadee S, Lumlertdacha B, Ampawong S, Tepsumethanon V, Shuangshoti S, Phumesin P, Asavaphatiboon S, Woraprukejaru L, Awhingsanon Y, Israsena N, Lafon M, Wilde H, Hemachudha T.Furious and paralytic rabies of canine origin: neuroimaging with virological and cytokine studies.J Neurovirol. 2008 ;14:119-29.
- Laothamatas J, Sungkarat W, Hemachudha T. Neuroimaging in rabies. Adv Virus Res 2011; 79: 309-27.
- Wilde H, Hemachudha T, Jackson AC.Viewpoint: Management of human rabies. Trans R Soc Trop Med Hyg. 2008; 102: 979-82.
- Wacharapluesadee S, Boongird K, Wanghongsa S, Ratanasetyuth N, Supavonwong P, Saengsen D, Gongal GN, Hemachudha T. A Longitudinal Study of the Prevalence of Nipah Virus in Pteropus lylei Bats in Thailand: Evidence for Seasonal Preference in Disease Transmission. Vector Borne Zoonotic Dis 2009; E pub: April 29.

Rabies Pathophysiolgy

Why we need to know?

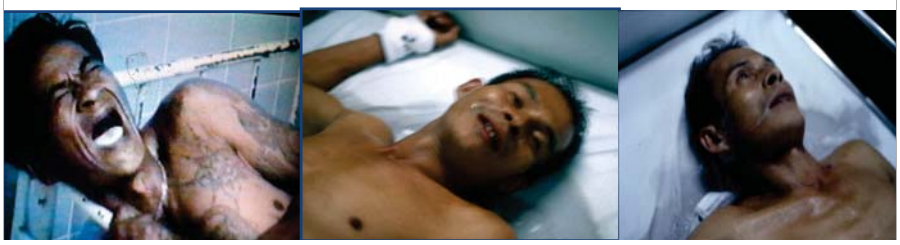
T. Hemachudha
Chulalongkorn University
WHO cc. Viral Zoonoses
Bangkok, Thailand

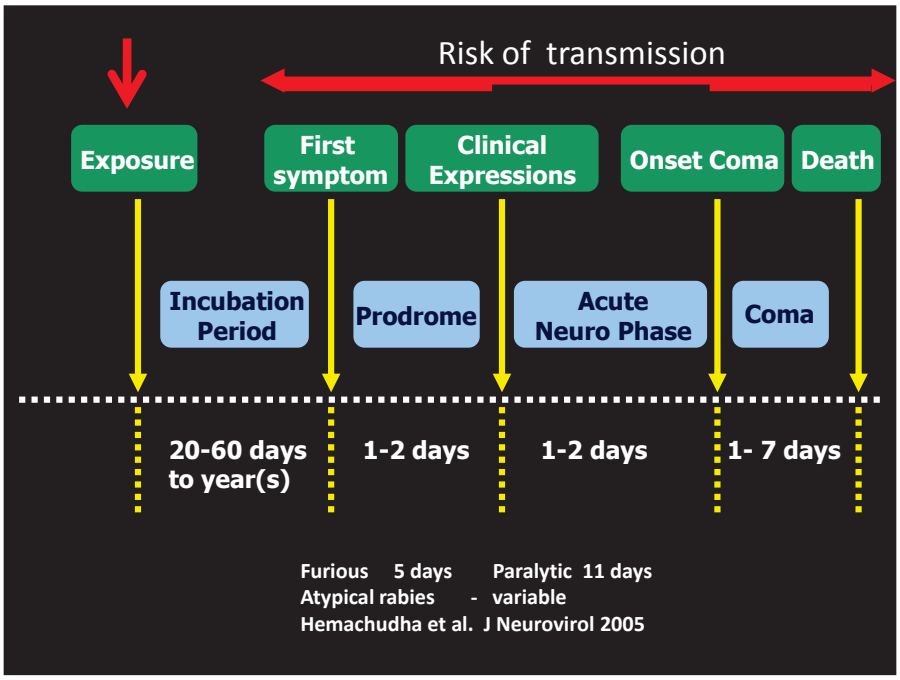




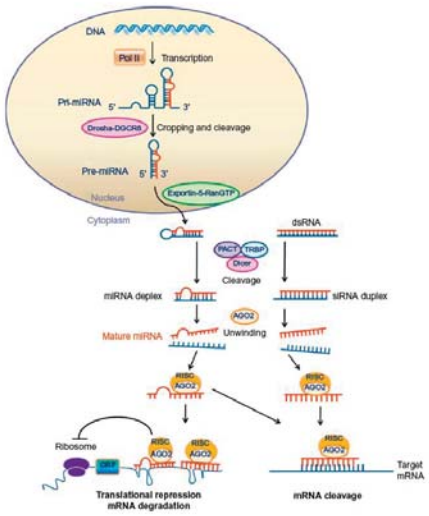
Why we need to know?

- *Prevention of infection, professional hazards*
- *Strict adherence to WHO recommendation*
- *Model to understand CNS infections*
- *Further development of diagnostic and therapeutic strategies*



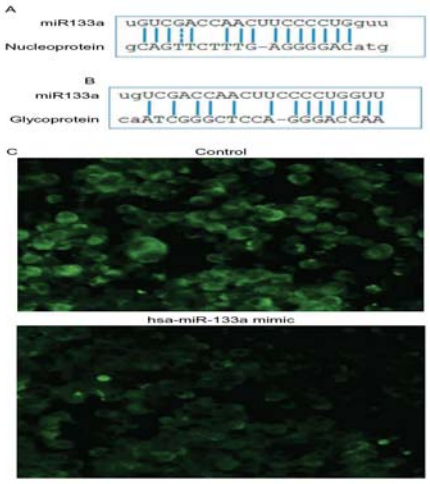


Eclipse Phase



Risk 1: Eclipse Phase

Treat as if this happened yesterday

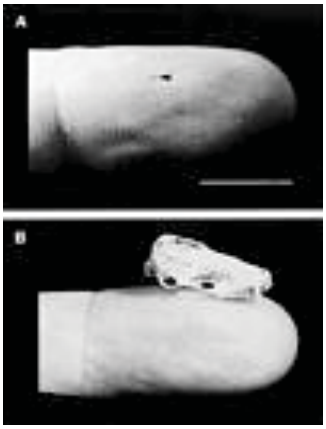


Israsena, Mahavihakanont, Hemachudha. Adv Virus Res 2011

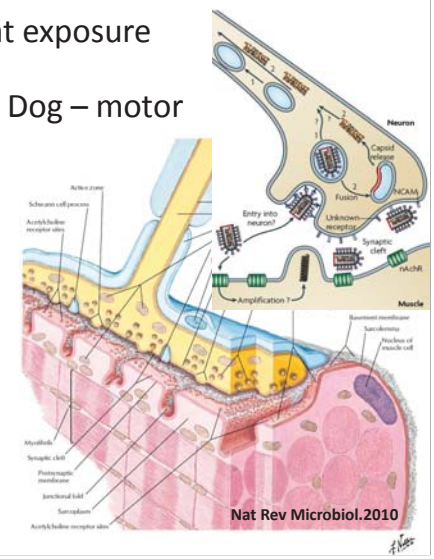
RISK-2

- RIG required only in case of severe wound
- Mucous membrane and bat exposure

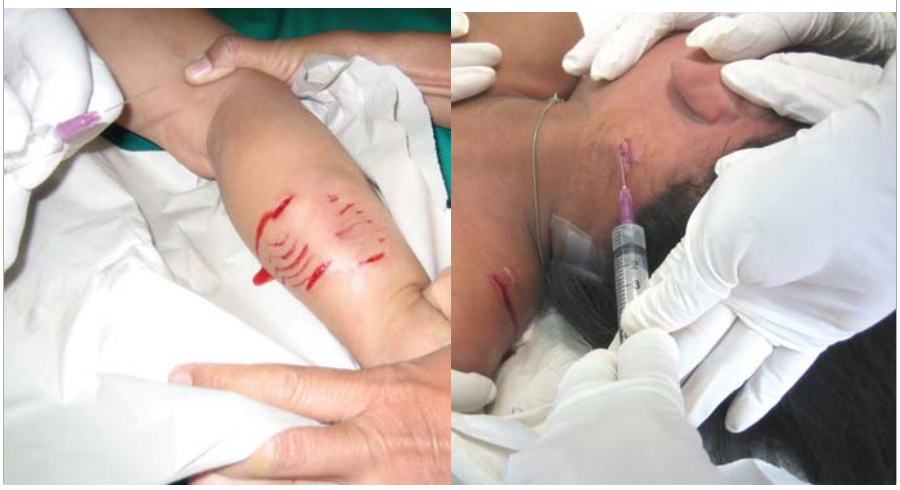
Bat variant- sensory



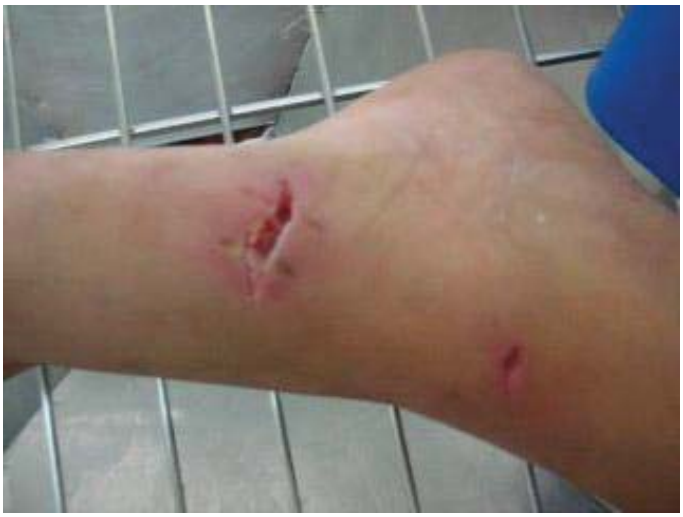
Dog – motor



Wound with bleeding needs RIG regardless of site



Wound (even infected) at the foot needs RIG



RISK-3

not able to recognize during PRODROMAL PHASE

- **Viruses are all over the brain and body (and transmission occurs) before brain symptoms develop**

RESEARCH LETTERS

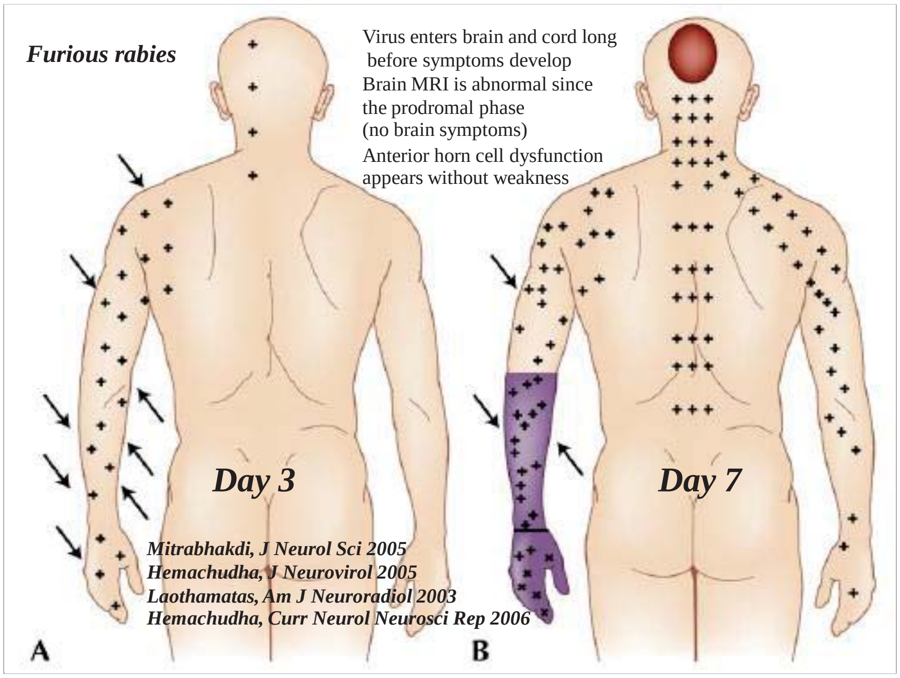
Nucleic-acid sequence based amplification in the rapid diagnosis of rabies

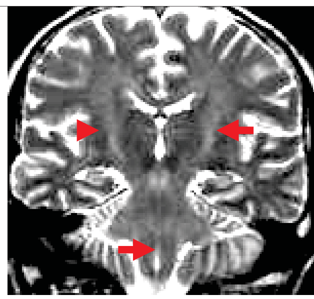
Supaporn Wacharapluesadee, Thiravat Hemachudha

Current serological tests do not reliably diagnose rabies. We describe a technique based on amplification of nucleic-acid sequences to detect rabies-specific RNA in the saliva and cerebrospinal fluid (CSF) of four living patients with rabies. Rabies RNA could be detected in either saliva or CSF, or both, in all patients and as early as day 2 after onset of symptoms. Both saliva and CSF should be serially tested because not every sample can be expected to be positive. The whole process, including automated extraction, isothermal amplification, and detection can be done within 4 h.

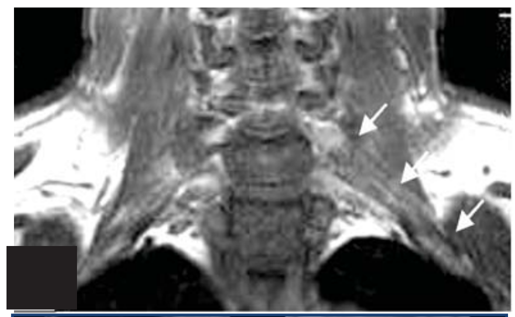
Lancet 2001; **358**: 892–93

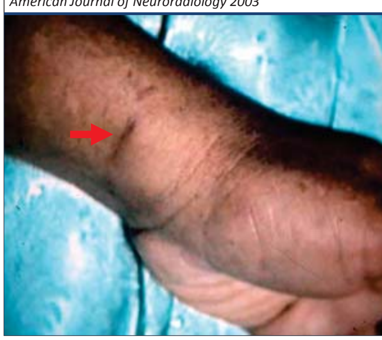
Rupprecht, Hanlon, Hemachudha. Lancet Infect Dis 2002
Hemachudha, Laothamatas, Rupprecht. Lancet Neurology 2002

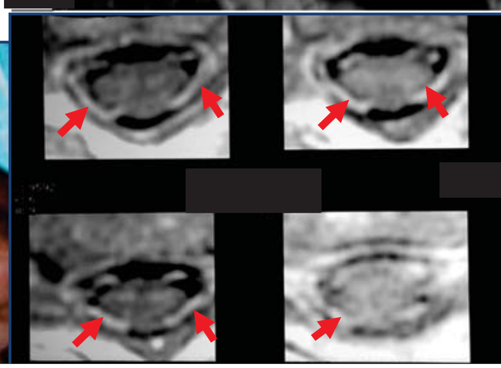


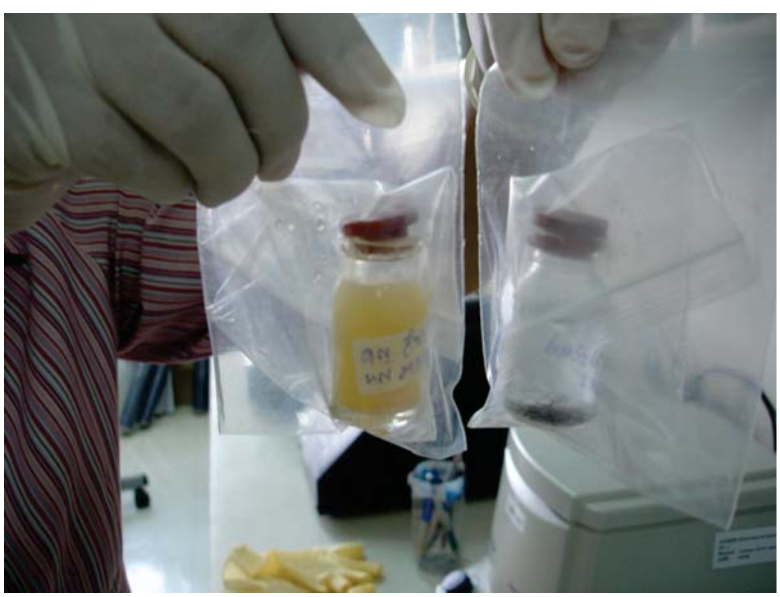


Laothamatas, Hemachudha, Mitrabhakdi, Wannakrairot, Tulyadaechanont. MR Imaging in human rabies. *American Journal of Neuroradiology 2003*

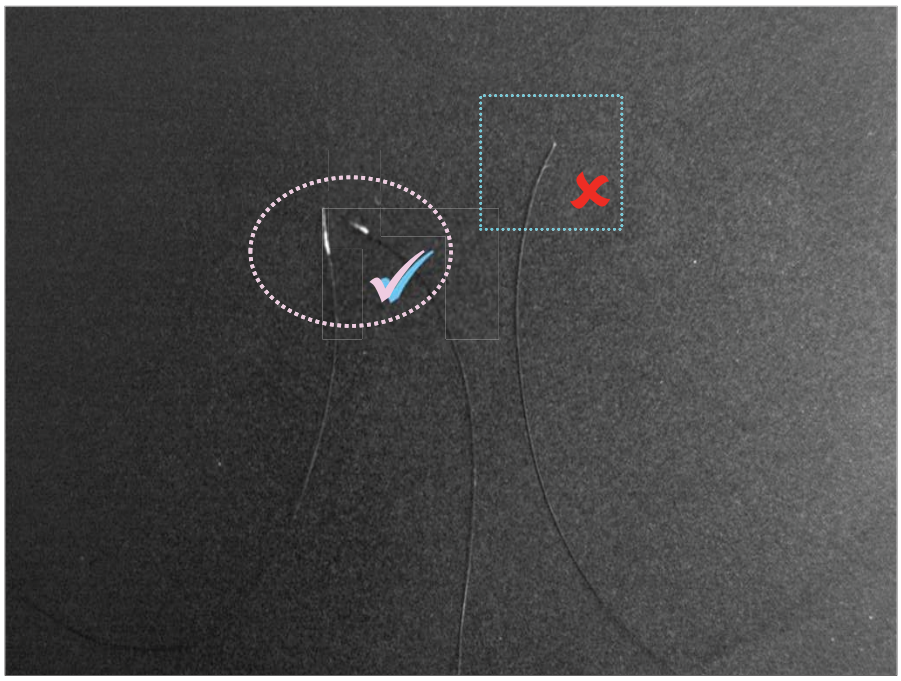








Saliva-urine-CSF-extracted hair follicles or skin biopsy at neck with hair follicles



Hospitalized day	Specimen	Results	
		NASBA	qRT-PCR** (copies/ml)
1	saliva	negative	ND*
	hair follicles	positive	43.3
2	saliva	positive	6,410
	hair follicles	negative	0
3	saliva	positive	102,000
	hair follicles	positive	0
4	saliva	positive	171,000
	hair follicles	positive	0
5	saliva	positive	75,900
	hair follicles	negative	0
6	saliva	positive	242,000
	hair follicles	negative	0
7	saliva	positive	67,400
	hair follicles	negative	ND*
8	saliva	positive	432,000
	hair follicles	negative	ND*

Hemachudha et al. J Neurovirol 2006
Wacharapluesadee and Hemachudha. Expert opinion 2010

GREATER AMOUNT OF VIRUSES IN FURIOUS DOG

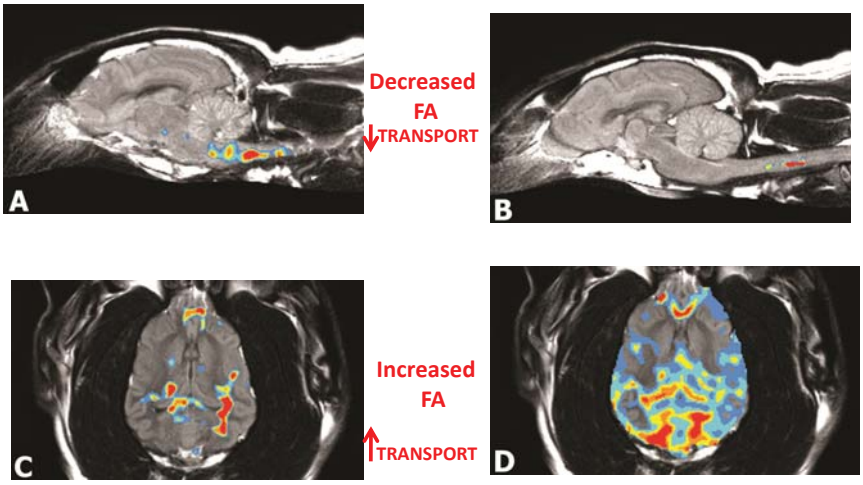
Table 1 Distribution of rabies viral RNA in CNS of rabid dogs

Brain region	Early		Late	
	Furious* ($n = 4$)	Paralytic* ($n = 4$)	Furious ($n = 1$)	Paralytic ($n = 1$)
Frontal	6.73 ± 2.68	0.48 ± 0.33	5.20	ND**
Temporal	6.69 ± 1.89	1.48 ± 0.92	5.00	7.30
Hippocampus	6.15 ± 2.03	0.95 ± 0.55	7.90	6.00
Parietal	6.40 ± 1.85	0.88 ± 0.69	4.00	4.60
Occipital	7.15 ± 3.73	0.13 ± 0.07	5.60	3.90
Midbrain	10.92 ± 3.36	1.87 ± 1.07	16.10	6.60
Pons	3.96 ± 1.14	1.51 ± 0.90	5.30	3.60
Medulla	7.07 ± 2.55	1.64 ± 0.98	15.30	2.90
Cerebellum	3.14 ± 1.09	0.43 ± 0.24	4.20	6.30
Thalamus	11.02 ± 2.78	2.66 ± 1.53	4.80	8.60
Basal ganglia	8.52 ± 2.04	5.74 ± 3.43	7.80	12.90
Caudate nucleus	10.59 ± 3.95	4.56 ± 2.63	9.70	13.90

Note. Viral RNA distribution is given as [(copies/μg total RNA) $\times 10^8$].
*Expressed as mean ± standard error of the mean.
**Sample not available.

Laothamatas et al, J Neurovirol 2008

paralytic furious

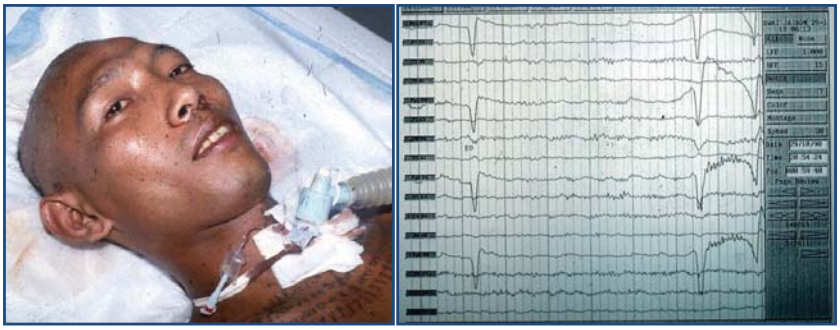


Demonstration best visualized by diffusion tensor imaging (Fractional Anisotropy)
Laothamatas, Sungkarat, Hemachudha. Adv Virus Res 2011

RISK-4

many variations; does not look like rabies

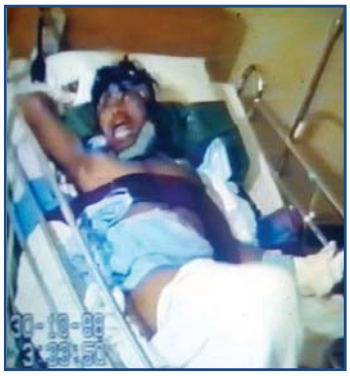
False negative PCR results on saliva-urine-CSF-hair follicles usually found in paralytic rabies

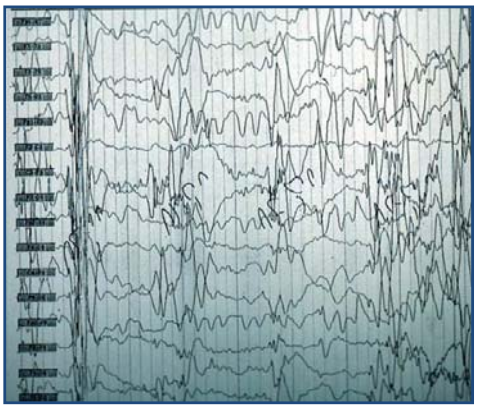


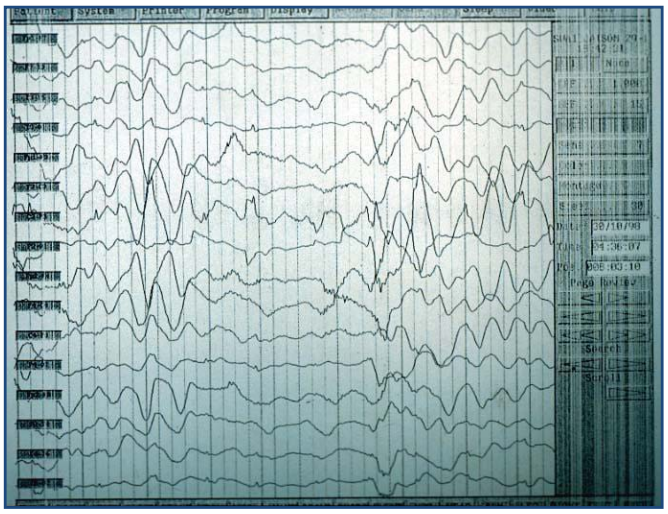
PARALYTIC (DUMB) RABIES
Biopsy at right temporal lobe revealed numerous FA positive particles

Paralytic vs. Furious Rabies

Furious rabies
Abnormal EEG only when aggression starts







Failure of Rabies Postexposure Prophylaxis In Patients Presenting with Unusual Manifestations

Prapimporn Shantavasinkul,[1] Terapong Tantawichien,[1,4] Supaporn Wacharapluesadee,[2] Anuruck Jeamanukoolkit,[5] Piyada Udomchaisakul,[1] Pairoj Chattranukulchai,[4] Patarapha Wongsaroj,[1] Pakamatz Khawplod,[1] Henry Wilde,[2,3] and Thiravat Hemachudha[2,4]

Clinical Infectious Diseases 2010;50:77–9

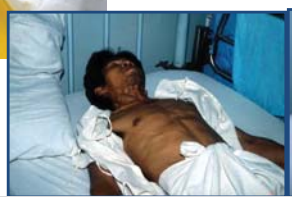
Dog bites-hands and knee 25 days earlier

State of the art PEP

Presenting with trismus and ophthalmoparesis

Later developed weakness of all limbs

True tetanus

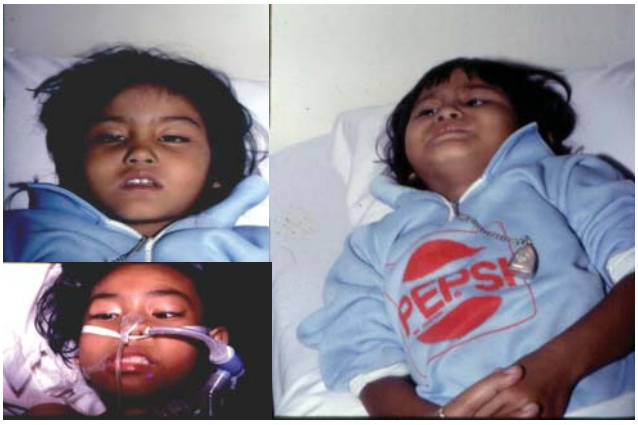


RISK – 5

- Viruses remain viable
- Laboratory and postmortem setting
- **ORGAN TRANSPLANTATION**
- **LABORATORY BIOSAFETY**
- **AUTOPSY**

RISK – 6

- Misunderstanding as treatable disease
- Survivors: 1972, 2004, 2010, 2011 had early antibody responses



2009 and 2010 cases; no virus/RNA found

- 2009 abortive infection – no ICU treatment

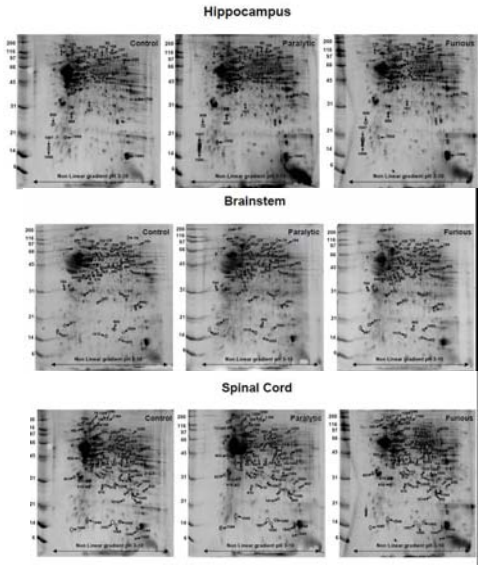
  Had serum and CSF IgG non-neutralizing antibodies
- 2010 ICU care – had serum and CSF IgG/IgM non-neutralizing antibodies
- Other immune mediator arms to clear viruses?

TABLE I Cases of human rabies with treatment failures that used the main components of the "Milwaukee Protocol"

Case no.	Year of death	Age and sex of patient	Virus source	Country	Reference
1	2005	47 male	Kidney and pancreas transplant (dog)	Germany	Maier *et al.* (2010)
2	2005	46 female	Lung transplant (dog)	Germany	Maier *et al.* (2010)
3	2005	72 male	Kidney transplant (dog)	Germany	Maier *et al.* (2010)
4	2005	Unknown	Dog	India	Bagchi (2005)
5	2005	7 male	Vampire bat	Brazil	–[a]
6	2005	20–30 female	Vampire bat	Brazil	–[a]
7	2006	33 male	Dog	Thailand	Hemachudha *et al.* (2006)
8	2006	16 male	Bat	USA (Texas)	Houston Chronicle (2006)
9	2006	10 female	Bat	USA (Indiana)	Christenson *et al.* (2007)
10	2006	11 male	Dog (Philippines)	USA (California)	Christenson *et al.* (2007)
11	2007	73 male	Bat	Canada (Alberta)	McDermid *et al.* (2008)
12	2007	55 male	Dog (Morocco)	Germany	Drosten (2007)
13	2007	34 female	Bat (Kenya)	The Netherlands	van Thiel *et al.* (2009)
14	2008	5 male	Dog	Equatorial Guinea	Rubin *et al.* (2009)
15	2008	55 male	Bat	USA (Missouri)	Pue *et al.* (2009), Turabelidze *et al.* (2009)
16	2008	8 female	Cat	Colombia	Juncosa (2008)
17	2008	15 male	Vampire bat	Colombia	Badillo *et al.* (2009)
18	2009	37 female	Dog (South Africa)	Northern Ireland	Hunter *et al.* (2010)
19	2009	42 male	Dog (India)	USA (Virginia)	Troell *et al.* (2010)
20	2010	11 female	Cat	Romania	–[b]

[a] Personal communication from Dr. Rita Medeiros, University of Para, Belem, Brazil.
[b] Personal communication from Dr. Mihai A. Turcitu, Institute for Diagnosis and Animal Health, National Reference Laboratory for Rabies, Bucharest, Romania.

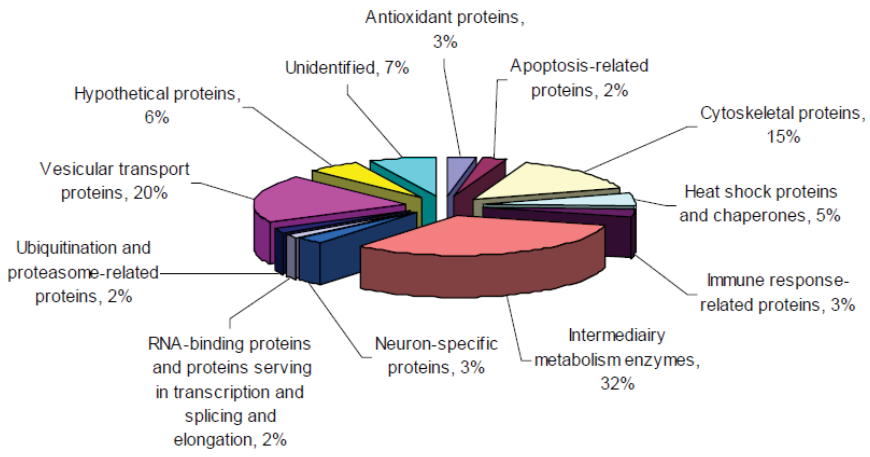
Jackson. Adv Virus Res 2011



Comprehensive proteome analysis of hippocampus, brainstem and spinal cord from paralytic and furious dogs naturally infected with rabies

Thanomsridetchai, Singhto,Tepsumethanon, Shuangshoti, Wacharapluesadee, Sinchaikul, Shui-Tein Chen, Hemachudha, and Thongboonkerd. (In Press)

Ongoing research using GLC-MS/MS Analysis against data on mRNA cyto-/chemokines transcripts in the brain and viral load at different regions



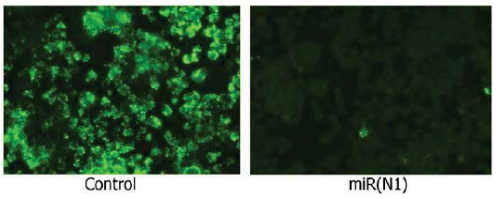
(i) anti-oxidants, (ii) apoptosis-related proteins; (iii) cytoskeletal proteins; (iv) heat shock proteins/chaperones; (v) immune regulatory proteins; and (vi) neuron-specific protein

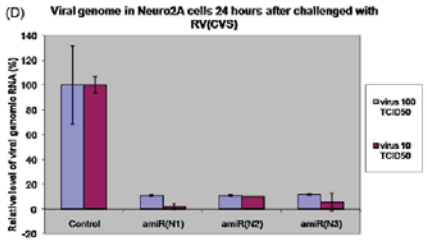
13, 17 and 41 proteins in hippocampus, brainstem and spinal cord, respectively, significantly differed between paralytic and furious forms, and thus may potentially be biomarkers to differentiate these two distinct forms of rabies.

Antiviral Research 84 (2009) 76–83
Contents lists available at ScienceDirect
Antiviral Research
journal homepage: www.elsevier.com/locate/antiviral

Inhibition of rabies virus replication by multiple artificial microRNAs

Nipan Israsena[a,*,1], Pornpan Supavonwong[b,1], Nittipol Ratanasetyuth[b], Pakamatz Khawplod[c], Thiravat Hemachudha[b]
[a] Department of Pharmacology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[b] Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[c] Queen Saovabha Memorial Institute, Thai Red Cross Society, Bangkok, Thailand





Israsena, Mahavihakanont, Hemachudha. Rabies virus infection and microRNAs. Adv Virus Res 2011

The Construction of pAAV-RFP and pAAV-RFP-miR

pAAV-RFP-miR

pAAV-RFP

Method

Neuro2a

↓

Transfect with pA

↓

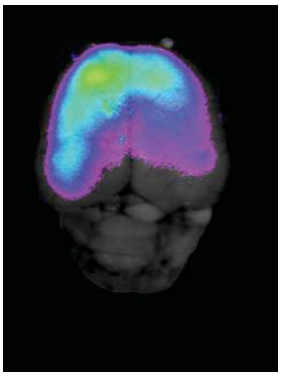
CVS (10^{-5})

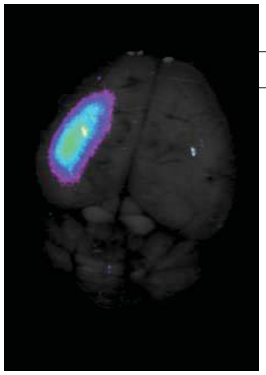
↓

Inoculate (IC) to mic
(Left frontal lobe)

Dr.Nipan Israsena
Dr.Aekkapol Mahavihakanont
Phatthamon Virojanapirom

Ex vivo imaging





Day 6 (Post-Inoculation)

Excited wavelength : 535 nm
Emitted wavelength : 600 nm

pAAV-RFP + CVS

pAAV-RFP-miR + CVS

- Intracerebral inoculation into left frontal lobe with approximately 1,000 transfected cells / 30 µl

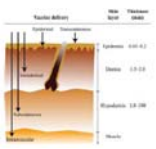
Dr.Nipan Israsena
Dr.Aekkapol Mahavihakanont
Phatthamon Virojanapirom

Post-exposure Prophylaxis

- *"Essen": 4 vs 5 doses regimen*
- *The one-week four-site PEP regimen ("4–4–4")*
- *A four-site one-day ID PEP for previously immunized individuals*

REGIMENS FOR POST-EXPOSURE TREATMENT

Regimen	Day 0 3 7 14 28	
Essen IM	1 -1 -1 -1 - (1)	(vial/site)
Zagreb (2-1-1) IM	2 - 0 -1 - 0 -1	(vial/site)
TRC-ID	2 - 2 - 2 - 0 - 2 4 - 4 - 4	(0.1 ml/site)



(0.1 ml of HDCV or PCEC or PVRV/site)

Pre-exposure Prophylaxis

- those working in rabies diagnostic or research laboratories, veterinarians, animal handlers (including bat handlers),
- animal rehabilitators and wildlife officers, as well as other people (especially children) living in or travelling to high-risk areas.
- Children under 15 years of age are the most frequently exposed age group, representing approximately 50% of human exposures in canine rabies-infected areas.

Pre-exposure Prophylaxis

- Pre-exposure vaccination is administered as one full dose of vaccine
- intramuscularly or 0.1 ml intradermally on days 0, 7 and either day 21 or 28

PERIODIC BOOSETER

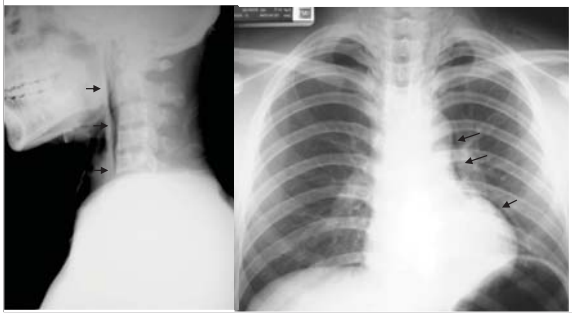
- Periodic booster injections are recommended for people who are at **continual risk**
- All people who work with live rabies virus in a diagnostic or research laboratory or in vaccine production should have periodic antibody determinations to avoid unnecessary boosters.
- People at continuous risk, e.g. rabies researchers, diagnostic laboratory workers (where virus is present continuously, often in high concentrations, and where specific exposures are likely to go unrecognized) should have serological testing **every 6 months.**
- A booster is recommended if the titre falls below 0.5 IU/ml.

Lack of phobic spasms sign; ignoring of the history
Rely on subcutaneous and mediastinal emphysema

300 hospital personels exposed

(operating room-surgical-medical wards and ER)

What should be the best mass accelerated PreP?
one ID site on Days 0, 3 and 7 ?
What should be the best 'antianxiety' protocol?



Kietdumrongwong, Hemachudha. BMC Infect Dis 2005

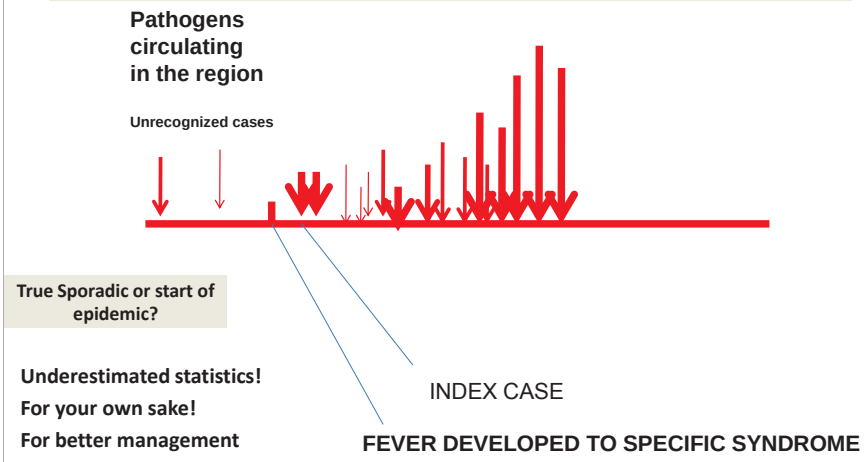
2,000 dogs saved from dinner tables
animal quarantine station
August 2011 Nakon Panom, Thailand

What should be the best mass accelerated PreP?

Emerging Zoonosis and Encephalitis

Thiravat Hemachudha, MD, FACP
Professor of Neurology
WHO cc. viral zoonoses
Chulalongkorn University
Bangkok, Thailand
www.cueid.org

What clinicians need to know?

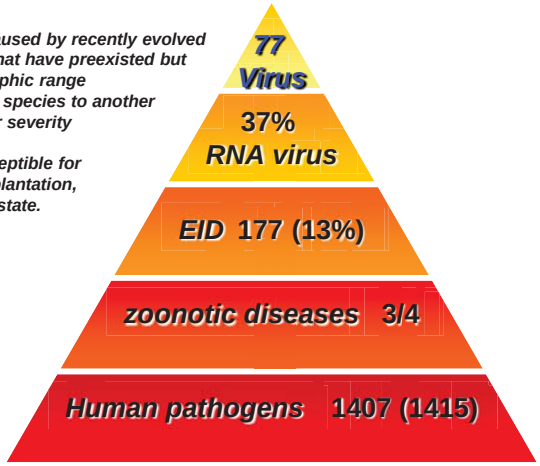


Underestimated statistics!
For your own sake!
For better management
For containment of spread

49% of emerging viruses cause encephalitis

Newly appeared or caused by recently evolved pathogens or those that have preexisted but
- Expanded in geographic range
- Move from one host species to another
-Increase in impact or severity

Host conditions susceptible for old agents eg. Transplantation, Immunosuppressive state.



Olival and Daszak. *J Neurovirol* 2005
Taylor LH, Latham SM,Woolhouse MEJ. *Phil Tran Rl Soc Lond B 2001*

Breaches in species barrier: selected emerging infections in humans identified since 1976




Infection	Animals linked to transmission	Year first reported
Ebola virus	Bats	1976
HIV-1	Primates	1981
E. coli O157:H7	Cattle	1982
Borreliosis	Deer	1982
HIV-2	Primates	1986
Hendra virus	Bats	1994
BSE/vCJD	Cattle	1996
Australian lyssavirus	Bats	1996
H5N1 influenza A	Chickens	1997
Nipah virus	Bats	1999
SARS coronavirus	Palm civets	2003
Ebola Reston virus	Swine	2009

Zoonoses in the Bedroom

Bruno B. Chomel and Ben Sun **EID 2011**

Table 2. Zoonoses acquired from close contact with pet, 1974–2010*

Zoonosis	Type of pet contact (reference)		
	Sleeping with	Kissing	Being licked by
Plague	Dogs (7), Cats (4–6)	–	–
Chagas disease	Dogs and cats (8)	–	–
Cat-scratch disease	Cats, kittens (10,12); dog (11)	–	Kittens (12)
Pasteurellosis	Dog (15)	Dog (13); dogs and cats (23,24); rabbit (24)	Dogs (16,18,21); cats (14,17,19,20,22); dogs and cats (14)
Capnocytophaga canimorsus septicemia	Cat (25)	–	Dog (25–27); cat (25)
Staphylococcosis	–	–	Dogs (28,29)
MRSA infection	Dog (30)	–	–
Rabies	–	–	Dogs (31–33)
Toxocariasis	Dogs and cats (1)	Dogs and cats (1)	Dogs and cats (1)
Giardiasis	Dogs and cats (1)	Dogs and cats (1)	Dogs and cats (1)
Cryptosporidiosis	Dogs and cats (1)	Dogs and cats (1)	Dogs and cats (1)
Cheyletiellosis	Dog (35)	–	–
Pet bites	Dogs (36,37)	–	–

*MRSA, methicillin-resistant *Staphylococcus aureus*; –, none reported.

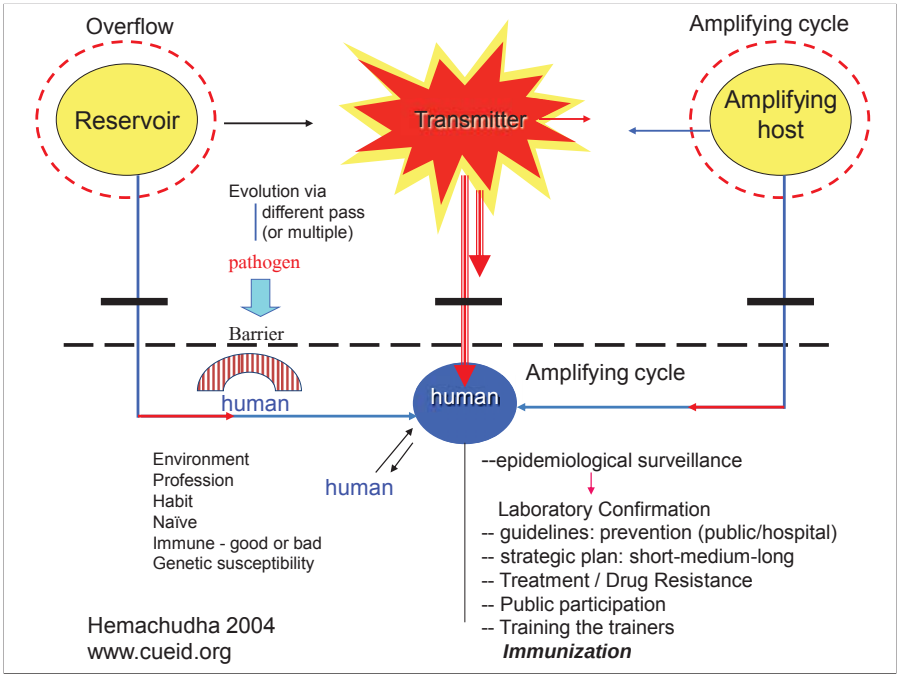
Table 4. Oral and Acquired Flora That May Be Associated with Cats.*

- Normal oral cavity
  - *Pasteurella multocida*
  - *Bartonella henselae*
  - Moraxella species
  - Staphylococci and streptococci
  - Anaerobes
- Acquired from soil and water environment
  - Leptospira species
  - Listeria species
  - Nocardia species
  - *Francisella tularensis*
- Mammals and birds
  - *Streptobacillus moniliformis*
  - *Erysipelothrix rhusiopathiae*
  - *Coxiella burnetii*
  - *F. tularensis*

* These flora may cause disease in a cat or be transiently carried orally or on claws.[1]

Case record 2010 NEJM cat bite

Figure 1. The transmission of *Francisella tularensis*.
F. tularensis is maintained in nature by interactions between animals and the ticks and flies that bite them. In recent years, more cases have been reported in humans from ticks and deerflies than from direct contact with wild animals. Spread occurs from wild-animal reservoirs to domestic animals, especially cats, and transmission to humans results from animal or insect bites, the handling of infected animal tissues, or inhalation of aerosolized organisms during activities such as landscaping or lawn mowing.



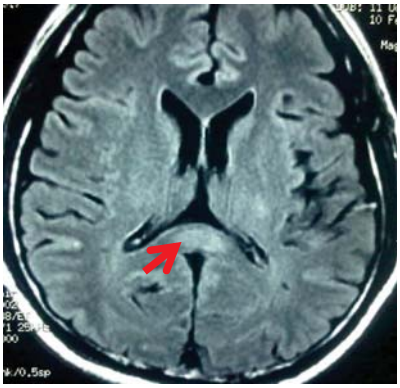
What clinicians need to know?

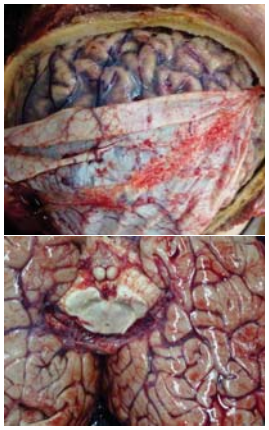
- No one knows exact incidence in most Asian countries !!
- How many could etiologies be identified?

Chulalongkorn University, Bangkok, Thailand

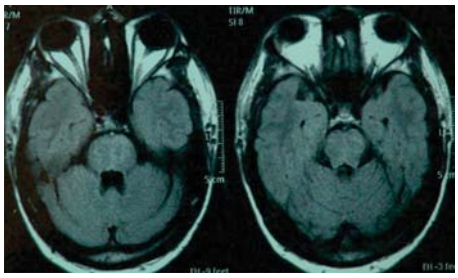
- Total 462 encephalitis patients
- Known pathogens : 207 patients (44.8%)
- Unknown pathogens : 255 patients (55.2%)

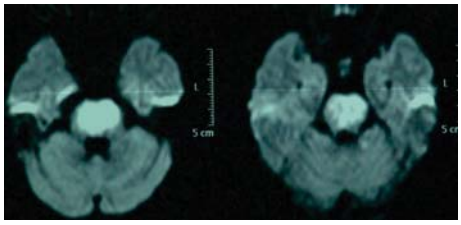
Masquerade with fever and petechial hemorrhages for 3 days followed by coma and intractable seizures



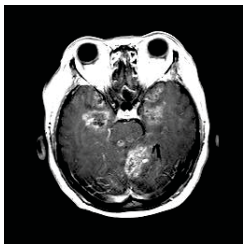


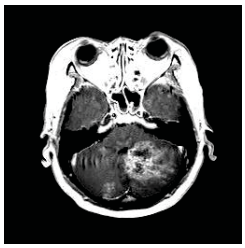
Fever-headache-left sided weakness-coma in 3 days

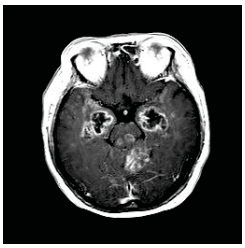


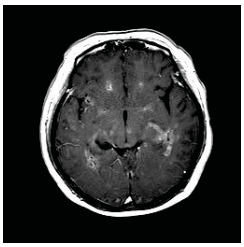


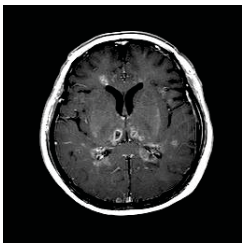
Cytotoxic edema
Restricted diffusion











Pathogen Signatures

- Timing - seasonal preference?
- Concurrence with the vector abundance?
- Associated illnesses in animals
- Geographic regions
- Rapidity of spread
- Comorbid status & underlying disease
- Contact history : animals humans
- Travel history within 1 month
- Demographic data
- Any particular risk groups
- Clinical Pattern - prodrome; pure neuro-/multiple organ or systemic involvement and encephalitis associations
- Time from onset to neurological illness
- Time from neurological onset to maximum
- Clinical severity-Mortality
- Neuroimaging

Various syndromes

Organ failure/involvement- always consider primary or secondary !!!

- **Acute febrile illness**
- **Acute fever + nervous system (+/- eye)**

1. Meningitis
2. Brain
3. Spinal cord
4. Cranial/spinal nerves

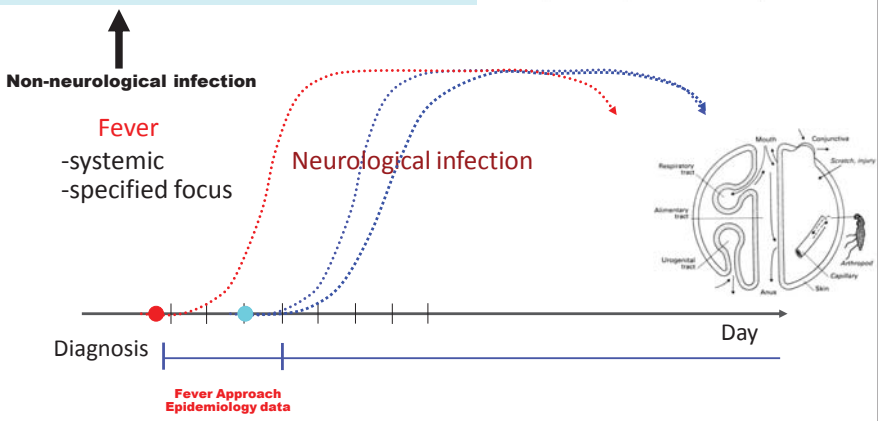
Primary nervous system pathogen

- **Acute fever +**

1. Liver (cholestasis/hepatitis)
2. Kidney
3. liver + kidney
4. Lung
5. Bleeding (Plt or coag)
6. Muscle
7. Nervous system
8. combination

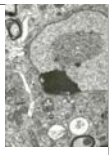
Nonspecific - myalgia arthralgia (systemic) LN liver spleen rash
Specific - diarrhea (GI) pyelonephritis (UTI) pneumonia hemorrhagic-fever

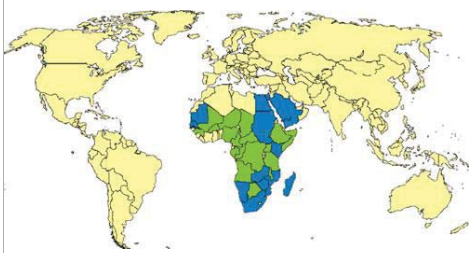
The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America



Brain may be an innocent bystander (from immune mechanisms or systemic complications, such as, metabolic, cardiovascular compromise, bleeding)

Rift valley fever





Animal species: Degree of severity

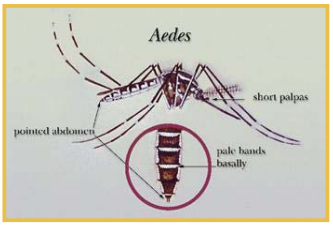
Mortality 100%	Severe Illness Abortion Mortality	Severe Illness Viremia Abortion	Infection Viremia	Refractive to Infection
Lambs	Sheep	Monkeys	Horses	Rodents
Calves	Cattle	Camels	Cats	Rabbits
Kids	Goats	Rats	Dogs	Birds
Puppies	Humans	Squirrels	Monkeys	
Kittens				
Some rodents				

Rift Valley Fever in Humans

- Incubation period: 2-6 days
  - Inapparent or flu-like signs
    - Fever, headache, myalgia, nausea, vomiting
    - Recovery in 4-7 days
  - Retinopathy
  - Hemorrhagic fever
  - Encephalitis
- Overall mortality ~1%

Transmission

- Arthropod vector
  - Mosquitoes
    - *Aedes*
    - *Anopheles*
    - *Culex*
    - Others
- Biting flies possible vectors



- Other mode of transmission
  - Direct contact or Aerosol
  - Tissue or body fluids of infected animals
    - Aborted fetuses, slaughter, necropsy
  - Humans possible source of virus for mosquitoes

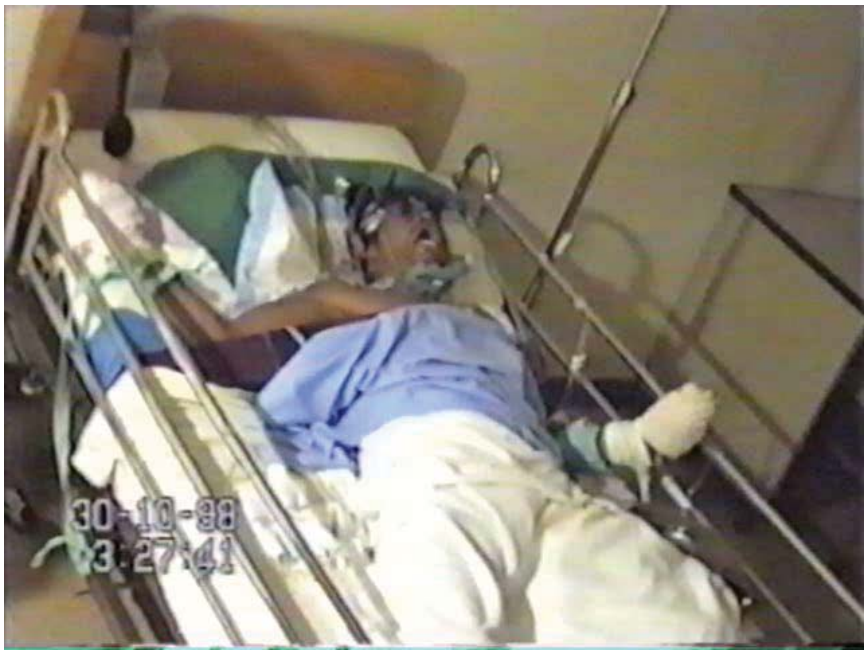
Significance

- Animals are part of ecosystem and source of livelihood for humans
- Zoonoses appears at human, animal and ecosystem interfaces
- More than 75% of emerging infectious diseases are zoonoses
- Trade and public health implication
- Many zoonotic diseases are vector-borne
- Most zoonoses are neglected
- Zoonotic agents are potential source of biological weapons

OBJECTIVES

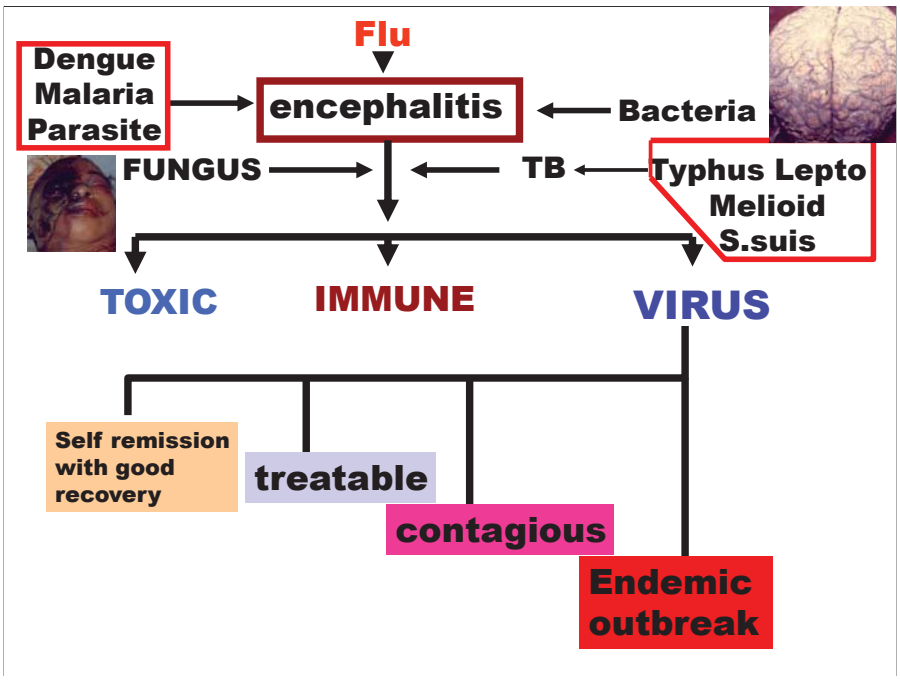
1. How to approach
2. **How to differentiate between usual and unusual* ones**

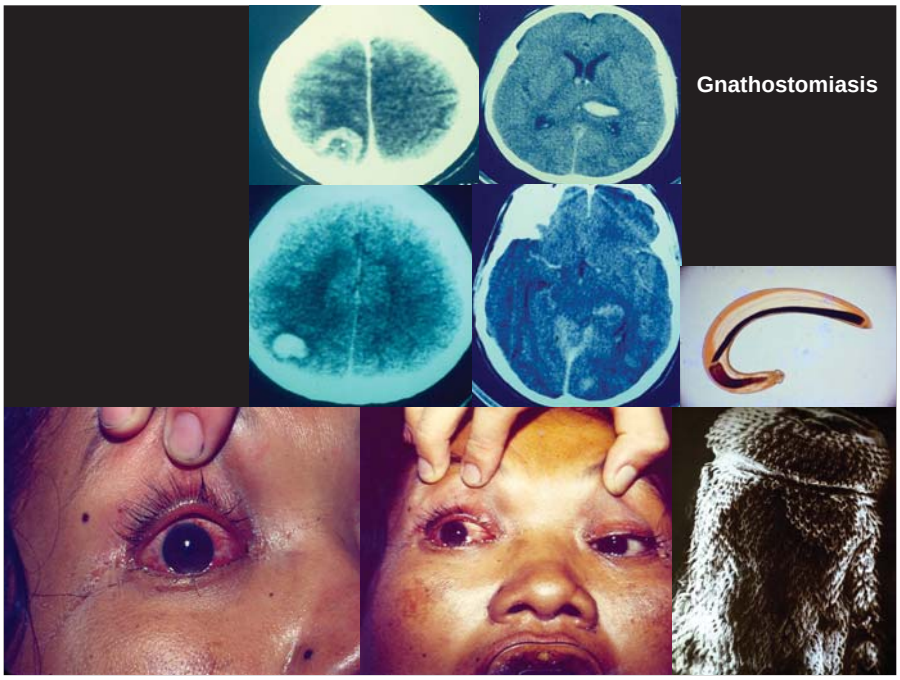
* Unusual = Potentially cause an outbreak or human-to-human transmission

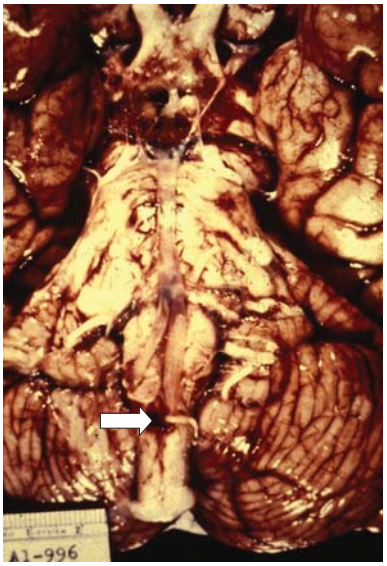


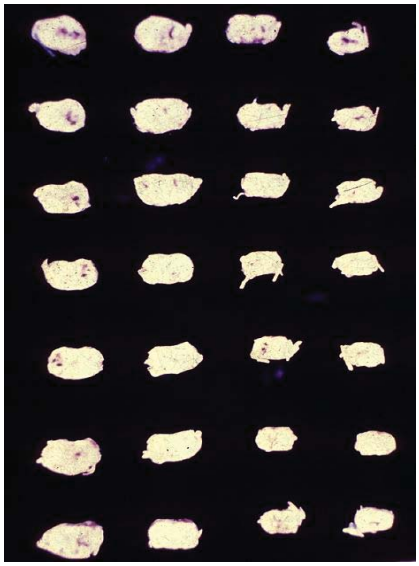
How to become an effective emerging CNS pathogen?

- **Severe impact**
  - national security
  - rapidly spread
  - high morbid/mortality
- **Maintenance system**
  - reservoir amplifying
  - transmitting vector
- **Able to Disguise**
  - different manifestations
  - as meningitis/encephalitis /myelitis
  - OR as pneumonia etc.
- **Escape notice**
  - normal CSF/ neuroimaging



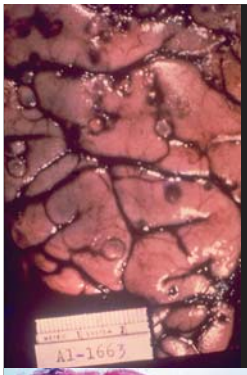






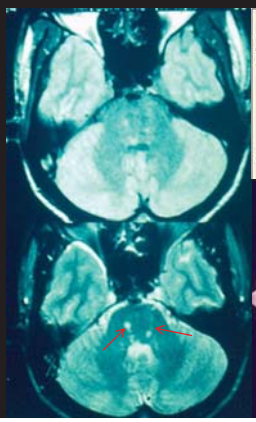
Gnathostomiasis

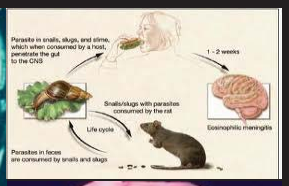
courtesy of Prof.Shanop Shuangshoti

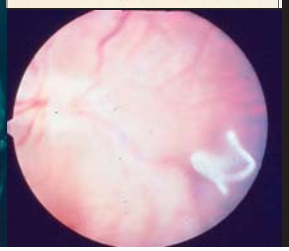


CYSTICERCOSIS

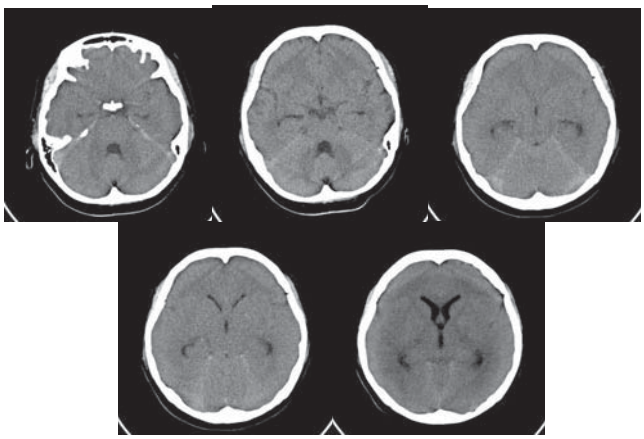
ANGIOSTRONGYLUS CANTONENSIS
Eosinophilic meningitis/encephalitis







Female 25 y.o. fever, scapular pain for 2 days then developed coma in 12 hours

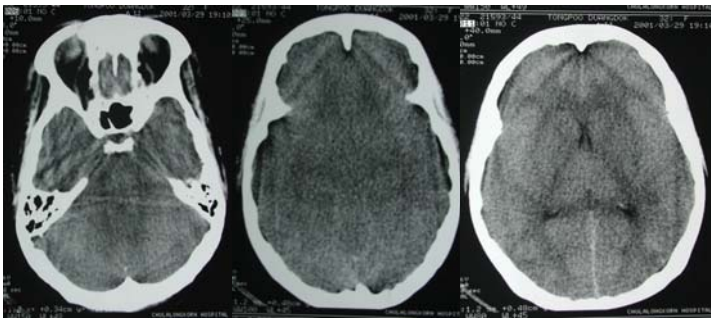


Brain edema with hydrocephalus previously reported in WNV case (Bosanko et al, 2003)
Anti HIV- neg CSF pressure 36; WBC 130 L 85% protein 861 sugar 96/161
PCR :TB, Herpes, WNV, JE, dengue, Nipah –negative

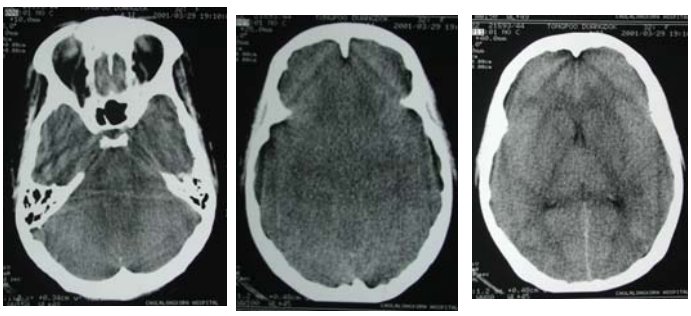
Neurology Quiz

A 24 year-old previously healthy women presented with a 2 day history of psychomotor retardation and headache but was still able to communicate correctly. She had a body temperature of 37.6 degree C and had no abnormal systemic examination findings. There were no focal neurological deficits nor papilledema. HIV serology was negative. CBC, renal and liver functions were within normal range. CSF examination revealed a pressure of 220 mm with no cells and normal sugar and protein levels. She became comatose 12 hours later.

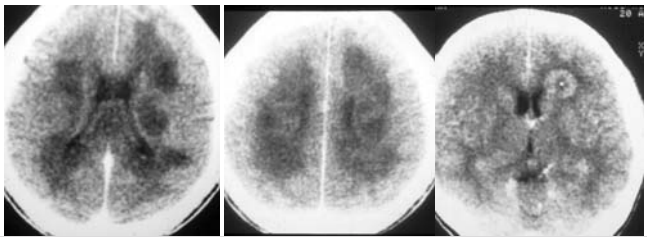
Her CT scan as shown



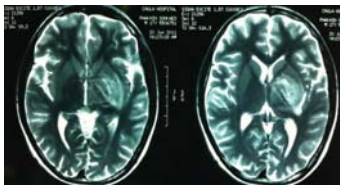
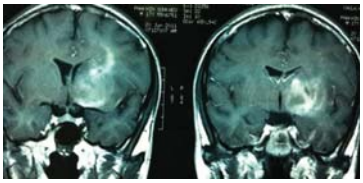
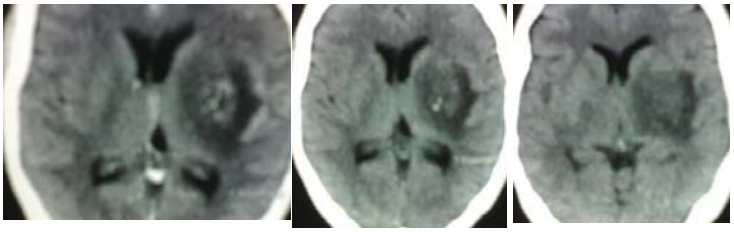
Toxic encephalopathy



Acute disseminated encephalitis



17 year-old male with diarrhea then fever and headache/right hemiparesis

Case summary

Female 18.

4 days PTA: fever and headache (vomitting) received ampicillin-Gentamicin-Cephalosporin

3 days PTA: fully conscious, inactive, mute, able to walk but with inappropriate behavior (urinate on the floor)

1 day PTA: fever deteriorated, bed bound, unable to follow command

Transferred to Chula Hospital

Physical Examination

BT 37.8, HR 60, BP 120/62, RR 14

- HEENT, CVS, Lungs, Abdomen – WNL

- Neurological exam:

Stiffneck + Global aphasia

Right homonymous hemianopsia

DTR brisk (Right)

Laboratory

- **CBC: Wbc 7650 (D/D normal), Hct 40%, Plt 450,000**
- **UA: normal creatinine: 1.1**
- **LFT: normal**
- **Chest X Ray: WNL**

Localization

- Behavioral change : temporal lobe
- Global aphasia : dominant parietal lobe
- Right homonymous hemianopsia : left parieto-occipital area
- Brisk DTR right side : left hemisphere

"left temporo-parieto-occipital lobe lesion"

36

Laboratory

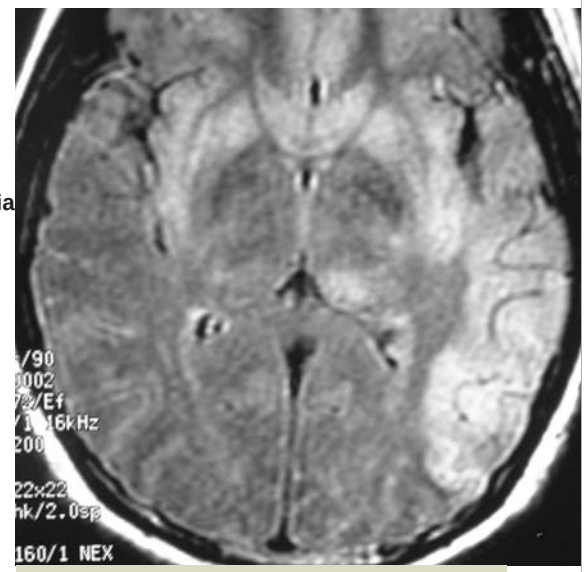
- **LP (1 days after onset):**

  Wbc 500 (Mono 98%), Rbc 10 Pandy + sugar 58/112
- **LP (4 days after onset):**

  OP/CP 29/17, pro 61, sugar 63 Wbc 130 (mono 100%)

Fever, global aphasia
R. homonymous hemianopsia
DTR asymmetry

Hemachudha (unpublished)



Chulalongkorn University Hospital

Laboratory Findings

- Dengue titers

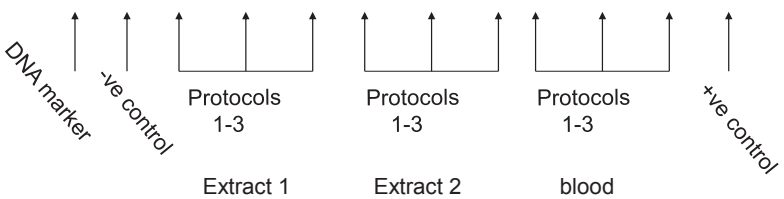
  (10 days after onset)

  CSF IgM 78 IgG 201

  serum IgM 24 IgG 122

  = Acute secondary Dengue infection

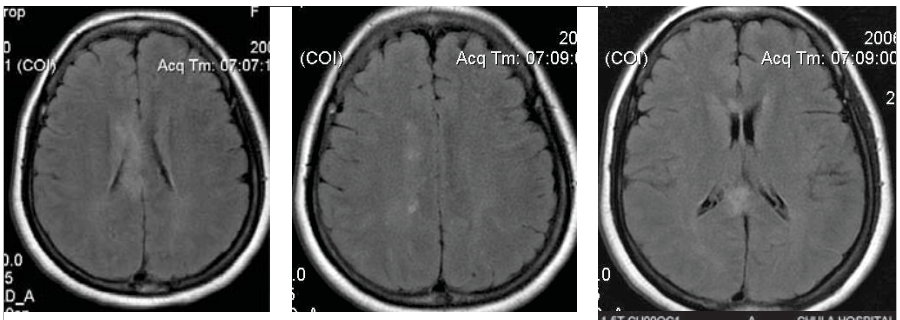
RT-nested PCR in CSF & blood



Courtesy of Dr. Kulwichit, Chulalongkorn Hospital

Bronnert et al. Complete ptosis and left arm weakness in dengue virus infected patient. Lancet 2005

Consultation to Chulalongkorn University Hospital

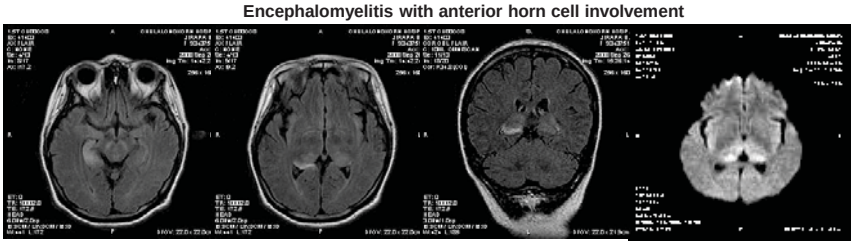


Dengue encephalitis
Chulalongkorn University Hospital
Callosal syndrome - anterior/ posterior

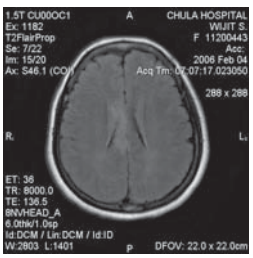
Hemachudha, unpublished

Dengue encephalitis

Encephalomyelitis with anterior horn cell involvement

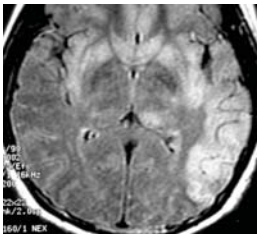


Callosal lesion disconnection syndrome



Hemachudha, unpublished

Right homonymous hemianopsia global aphasia



No specific pattern

Acute necrotizing encephalopathy in Flu
Fever, convulsions, coma die within 2-3 days

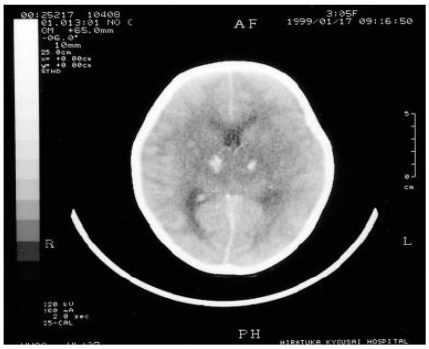


Fig. 1 Brain computed tomography images (case 1) taken on 17 January, 2 days after admission. Bilateral thalamic hemorrhage and peripheral low density areas can be seen.

Sugaya. Pediatr Inter 2000 H3N2

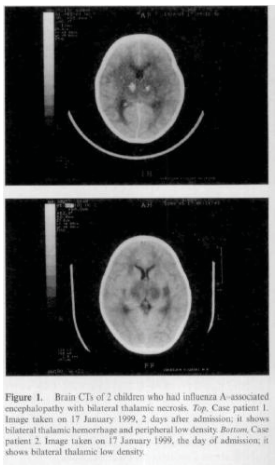


Figure 1. Brain CTs of 2 children who had influenza A-associated encephalopathy with bilateral thalamic necrosis. *Top*, Case patient 1. Image taken on 17 January 1999, 2 days after admission; it shows bilateral thalamic hemorrhage and peripheral low density. *Bottom*, Case patient 2. Image taken on 17 January 1999, the day of admission; it shows bilateral thalamic low density.

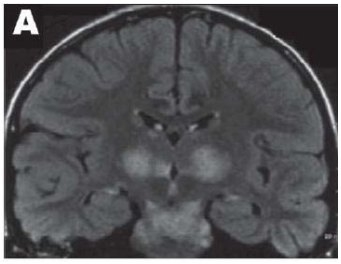
Shinjo, et al. CID 2000 H3N2

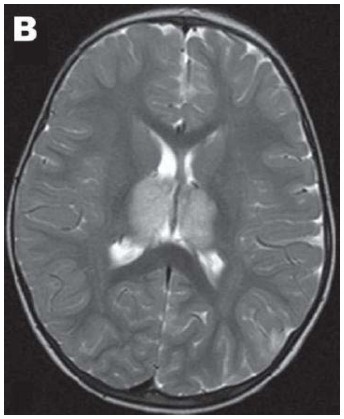
[redacted]

Novel Human Reovirus Isolated from Children with Acute Necrotizing Encephalopathy

Louise A. Ouattara, Francis Barin, Marie Anne Barthez, Bertrand Bonnaud, Philippe Roingeard, Alain Goudeau, Pierre Castelnau, Guy Vernet, Glaucia Paranhos-Baccala, and Florence Komurian-Pradel

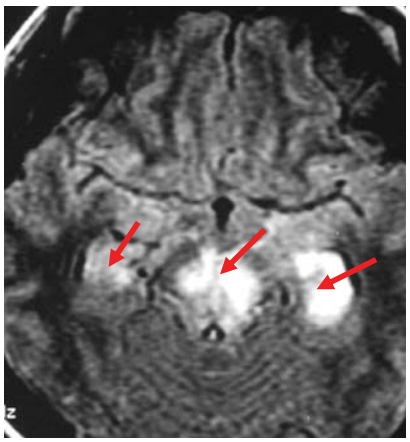
[redacted]

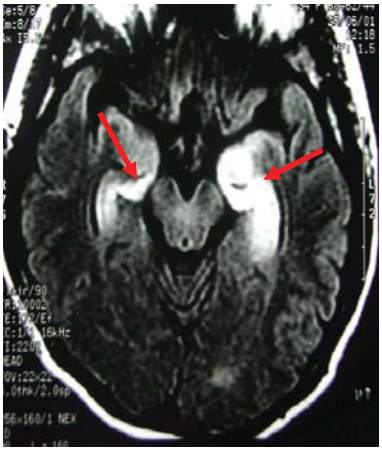




Japanese encephalitis

Herpes simplex encephalitis





History

- **Female 18 years of age, normal health status**

5 days: fever restless see ghosts

1 day : noticed having chewing and abnormal movement of facial muscles and later deepening of consciousness with limb weakness

47

Investigations

- CBC: WBC 17800 N86% L 5.9 % MOno 5.8 % Hct 39% Plt 353000
- BUN 16 Cr 0.9 Na 136 K 3.8 Cl 96 CO2 20.5
- Chol 176 DB 0.3 TB 1.5 AST 27 ALT 43 ALP 30 Alb 4.9 TP 8.8 Glob 3.9
- Ca 9.9 Mg 3.2
- BS 88

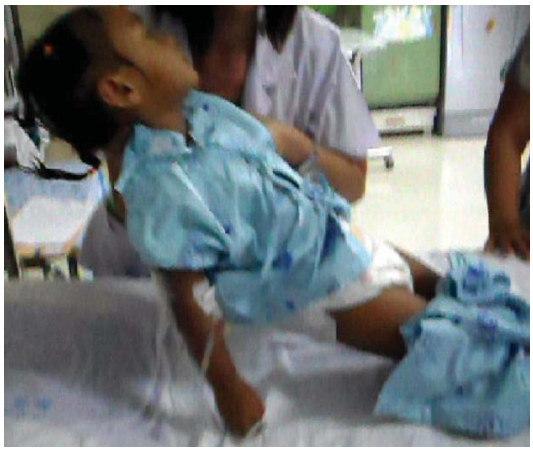
49

Investigations

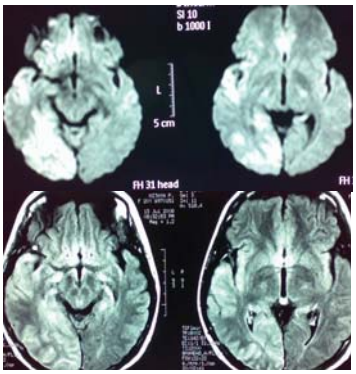
- Serum NMDA receptor antibody +ve (1:480)
- Other paraneoplastic panel : ANNA-1, ANNA-2, ANNA-3, PCA-1, PCA-2, PCA-Tr, GAD, Amphiphysin, CRMP-5, AMPA, GABA-b, VGKC, SRP-54) } all negative
- Serum Copper 145 (80- 155). Ceruloplasmin 31.32 (28-45)

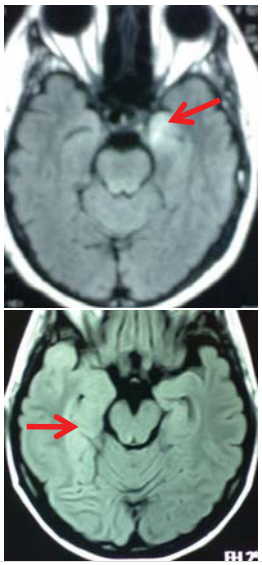
50

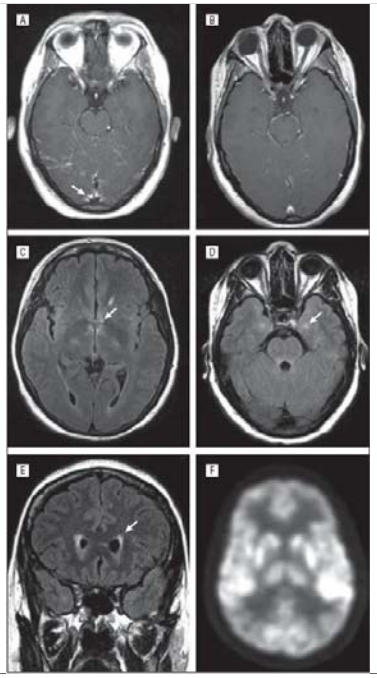
2 year-old fever, vesicular rashes hands/feet with generalized spasticity. Anti-AMPA2 antibody stiff person syndrome



MELAS versus HSV





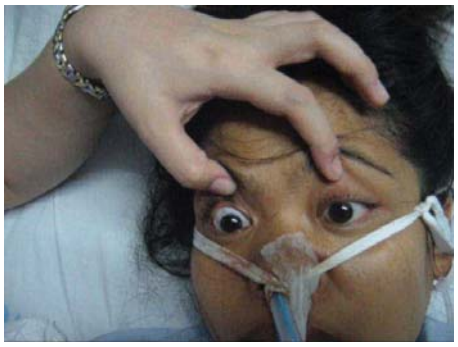


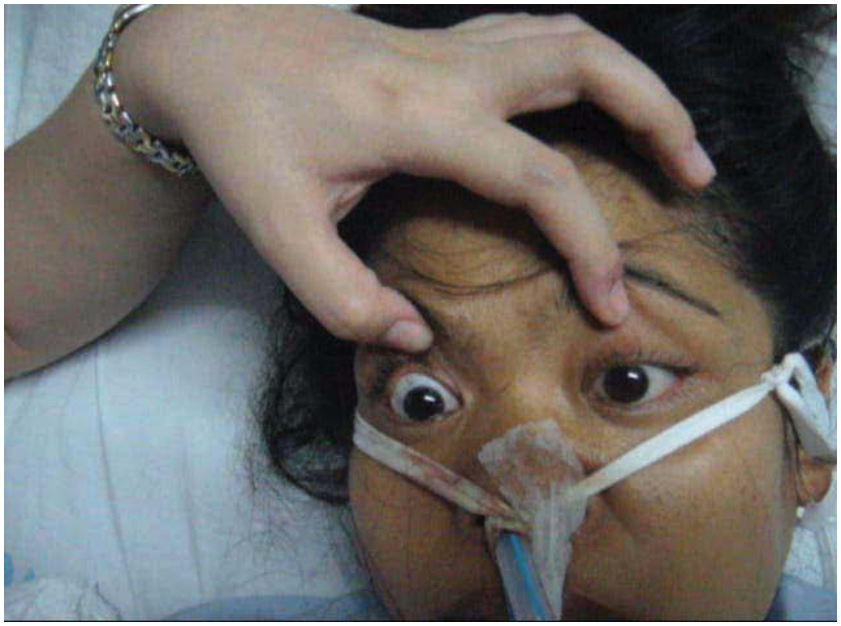
Smith et al. Arch Neurol 2011
Anti-NMDA receptor autoimmune encephalitis

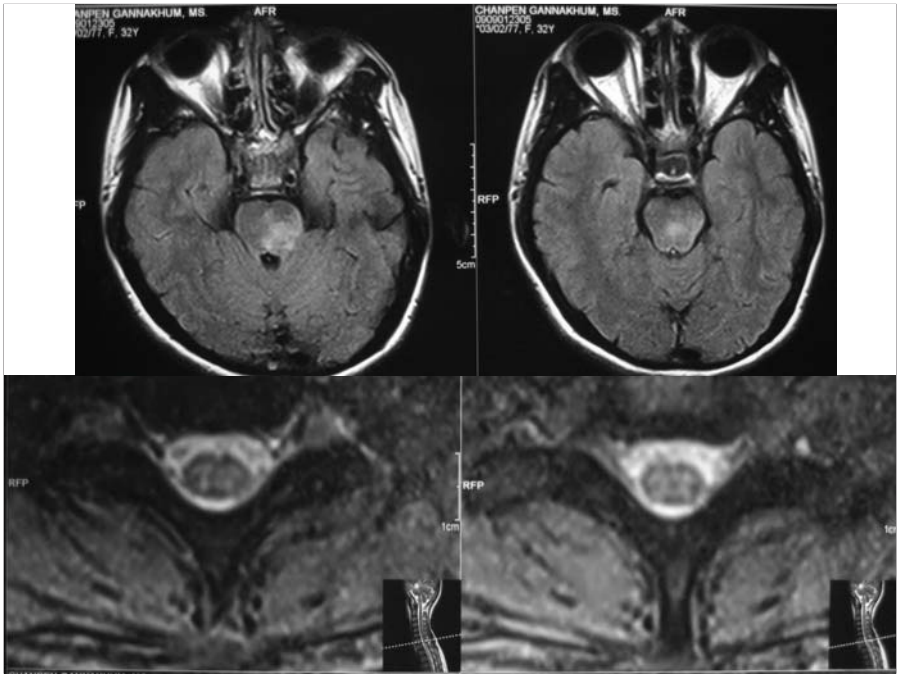
How thorough history and examination help?

- **Female 32 yrs old**
  CC : limb weakness 4 d PTA
- **20 d PTA low grade fever rhinorrhea**
- **14 d PTA nausea/vomitting hiccups headache**
- **8 d PTA numb feeling distal limbs**
- **4 d PTA vertigo no tinnitus could not inhibit urge to void**
- **3 d PTA urinary retention increasing vertigo facial palsy and dysarthia right hemiparesis then quadriparesis**

BT 38.5 °c , BP 111/77, PR 100
not pale, no jaundice
Lung /Heart/Abdomen - WNL
Ext : no edema
Upbeat nystagmus
Dysconjugate eyes
Right central facial weakness
quadriparesis
Diaphragmatic breathing, absent AJs





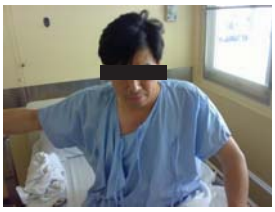


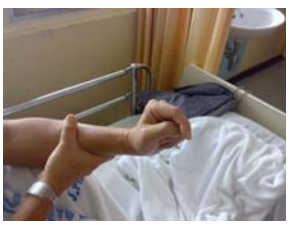
HERPES VIRUS INFECTION OF THE NERVOUS SYSTEM

Kleinschmidt-DeMasters and Gilden.Brain Pathol 2001

- ENCEPHALITIS – HSV1/2, VZV, CMV
- ACUTE MENINGITIS – VZV, HSV-2
- RECURRENT MENINGITIS – HSV-2
- COMBINATIONS OF MENINGITIS, ENCEPHALITIS, MYELITIS, RADICULITIS EBV
- MYELITIS – VZV, CMV, EBV, HSV-2
- VENTRICULITIS/ENCEPHALITIS – VZV, CMV
- BRAINSTEM ENCEPHALITIS – HSV, VZV
- POLYMYELORADICULITIS - CMV

PRESENTING WITH FEVER AND LEFT ARM WEAKNESS IN A WEEK





Chandipura virus

Reservoir: Horse Cattle Pig
Vector: None
Vehicle: Aerosol from animal
Incubation Period: 2d - 6d (range 1d - 8d)
Diagnostic Tests:
Viral culture (blood), Serology
Nucleic acid amplification.

Biosafety level 3.

Myalgia, headache, conjunctivitis, oral and digital vesicles
often follows animal contact
infection resolves within one week
no fatality or residua

Chandipura virus (India) associated with outbreaks of severe encephalitis.

1965: India
1997: United States
1998: United States
2002: India
2003: India
2004: Bolivia, India
2005: Bolivia, United States

Total outbreaks: 9
Total outbreak cases (approximate): 531

most recent in India 2005-6

A large outbreak of acute encephalitis with high fatality rate in children in Andhra Pradesh, India, in 2003, associated with Chandipura virus

B L Rao, Atanu Basu, Nileen S Wairagkar, Milind M Gore, Vidya A Arankalle, Jyotsna P Thakare, Ramesh S Jadi, K A Rao, A C Mishra

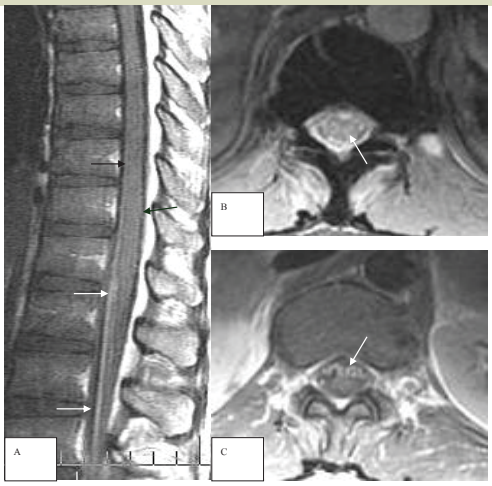
Summary

Background An outbreak of acute encephalitis of unknown origin with high case fatality (183 of 329 cases) was reported in children from Andhra Pradesh state in southern India during 2003. We investigated the causative agent.

183/329
Few days to coma
Age < 15
2003

Viral encephalitis is an important global public-health problem. In India, although many encephalitis outbreaks have been associated with Japanese encephalitis virus,[1] several outbreaks have remained undiagnosed. One such outbreak was documented in Jamshedpur as early as 1954.[2] A group of patients was characterised by sudden onset of high-grade fever (101–106°F), occasional vomiting, rigors, and drowsiness leading to unconsciousness, followed by death in 6–48 h. The age of the affected children ranged from 2·5 months to 15 years. The case fatality rate was 52·3%, and CSF findings were within normal limits. The cause was thought to be viral, but laboratory findings were inconclusive. Subsequently, outbreaks of a similar nature were described from Nagpur, Raipur, Bilaspur, and nearby areas of central India in the years 1958, 1965, 1968, 1978, and 1983. Similar outbreaks were reported from Warangal in Andhra Pradesh in 1997 and 2002. In the absence of a defined cause, these outbreaks were tentatively attributed to Reye's syndrome, dengue, chikungunya, Japanese encephalitis, measles, and so on.[3–5]

A 25-year-old Thai male presented with fever, headache and rapidly progressive paraparesis within a few days. He then became confused on the seventh day of illness. Three days later, he developed respiratory failure and was intubated and refered to Ramathibodi Hospital.



Courtesy of Dr.Laothamatas (Lancet 2004)

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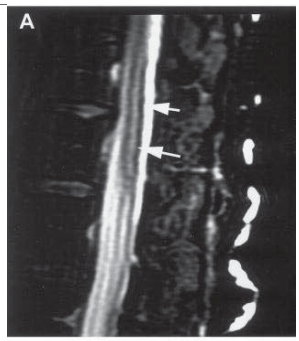


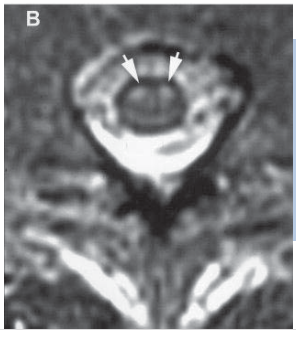


TABLE 1. MOTOR AND SENSORY AMPLITUDES.*

Nerve	Stimulation Site	Recording Site	Patient 1 Right	Patient 1 Left	Patient 2 Right	Patient 2 Left	Patient 3 Right	Patient 3 Left	Normal Values
Median motor nerve (mV)	Wrist	Abductor pollicis brevis	3.9	—	3.8	—	2.0	11.4	≥5.0
Median sensory nerve (μV)	Wrist	Second digit	20.4	—	34.4	—	33.4	35.4	≥20.0
Ulnar motor nerve (mV)	Wrist	Abductor digiti minimi	5.0	—	4.4	—	1.6	7.5	≥4.5
Ulnar sensory nerve (μV)	Wrist	Fifth digit	18.8	—	17.8	—	28.8	27.6	≥15.0
Musculocutaneous motor nerve (mV)	Erb's point	Biceps	2.4	—	—	—	0.2	7.6	≥4.0
Musculocutaneous sensory nerve (μV)	Elbow	Forearm	10.6	—	17.2	—	27.1	32.6	≥10.0
Axillary motor nerve (mV)	Erb's point	Deltoid	1.7	—	0.3	—	0.4	5.3	≥4.0
Radial sensory nerve (μV)	Forearm	Dorsum of hand	23.2	—	48.6	—	31.9	31.8	≥15.0
Peroneal motor nerve (mV)	Ankle	Extensor digitorum brevis	NR	4.2	1.2	0.1	—	—	≥2.0
	Knee	Tibialis anterior	0.2	2.8	—	0.4	—	—	≥4.0
Peroneal sensory nerve (μV)	Leg	Dorsum of foot	2.2	3.1	6.6	7.1	—	—	≥5.0
Tibial motor nerve (mV)	Ankle	Abductor hallucis	2.5	7.6	2.8	3.3	—	—	≥3.0
Sural sensory nerve (μV)	Posterior leg	Ankle	8.4	9.7	13.3	14.8	—	—	≥8.0

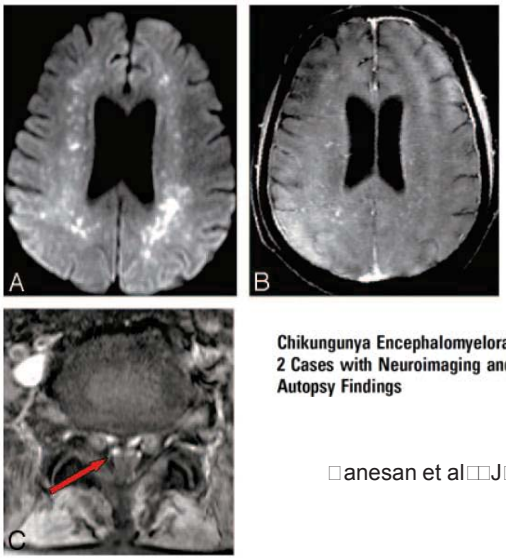
*NR denotes no response.

West Nile virus:

Anterior horn cell involvement

- **Reduction of motor amplitudes**
- **Preserved sensory responses**
- **Scattered denervations**

Leis et al./Glass et al. N Engl J Med 2002
Li et al. Ann Neurol 2003



Chikungunya Encephalomyeloradiculitis: Report of 2 Cases with Neuroimaging and 1 Case with Autopsy Findings

□anesan et al□□J□□ □□□□

Fig 1. *A*, Bilateral frontoparietal white matter lesions with restricted diffusion. *B*, Post-contrast enhancement on T1WI fat-saturated images and mild ventriculomegaly. *C*, Post-contrast T1WI fat-saturated axial images at the L4 level reveal enhancement of ventral nerve roots (*arrow*).

Emerging pathogens

- ***Enterovirus 71***
- ***Henipavirus***
- ***Chandipura virus***
- ***Lyssavirus***
- ***S.suis***
- ***Dengue***
- ***Flu***
- ***Arboviruses***

Pathogens

Predict will focus on pathogens most likely to have a significant public health impact, such as:

- Alphaviruses
- Bunyaviruses
- Coronaviruses
- Filoviruses
- Flaviviruses
- Lyssaviruses
- Orthomyxoviruses
- Paramyxoviruses
- Retroviruses
- Emerging pathogens

- **Male, 39 years old, teacher**

  5 days - fever

  4 days- fatigue, shaking limbs, dizzy, cough

BT 39 C, PR 124/min, RR 36/min

Lethargic, barely respond to command.

gaze paretic nystagmus with anisocoria

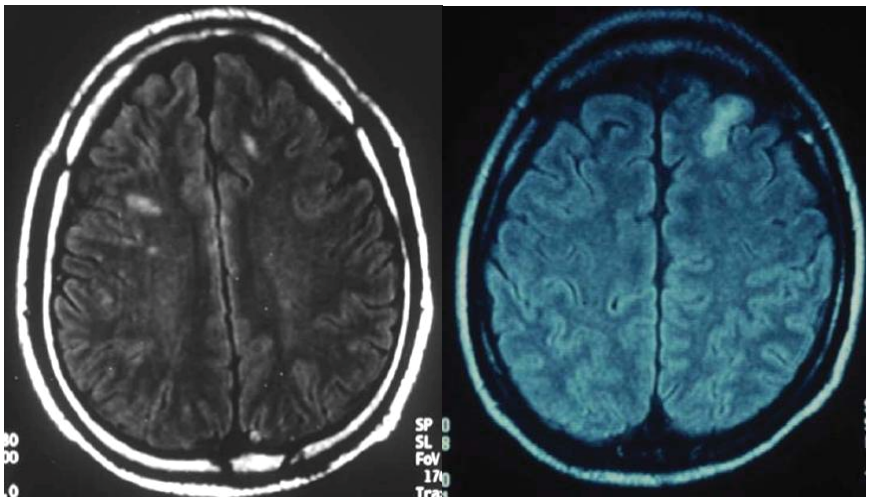
(Rt 4, Lt 2 sluggish), hiccups

Hypotonia with depressed reflexes

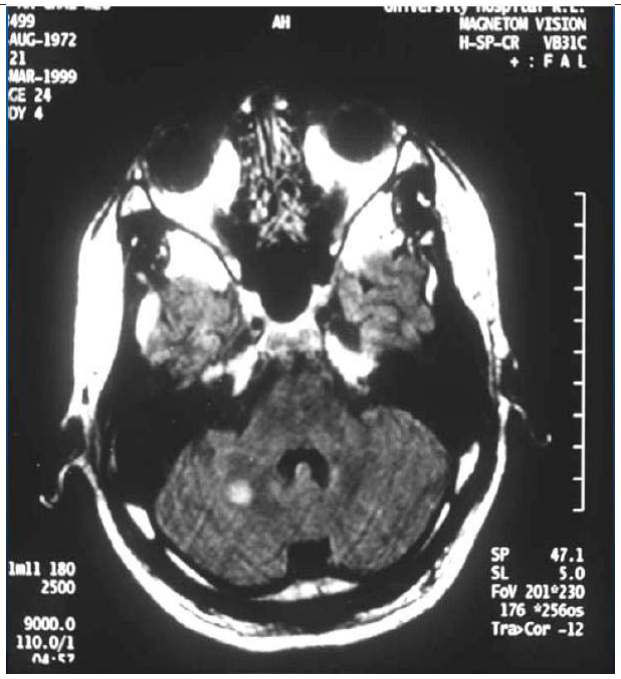
Segmental myoclonus of both legs

Up-going toes (bs)

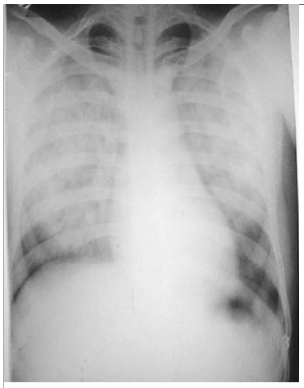
□im□late□case □r teachin□ □ase□ □n □ata □r□m □r□□□an



Prof.Tan



Prof.Ta



Hossain et al, 2008

Human to human transmission, more effectively in patient with associated pneumonia

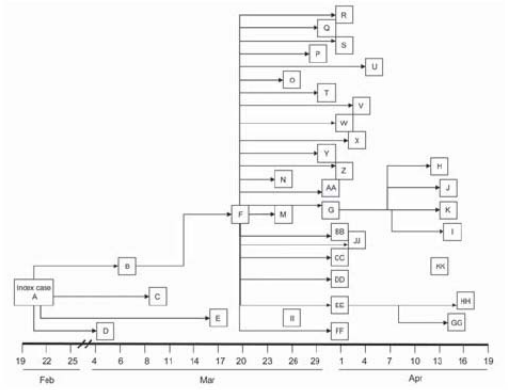


Figure 2. Chain of person-to-person transmission with dates of onset of illness during a Nipah virus outbreak, Faridpur District, Bangladesh, 2004. Letters identify individual patients. Patients KK and II had no known contact with any ill patient before their illness.

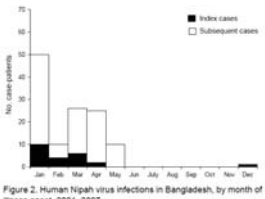
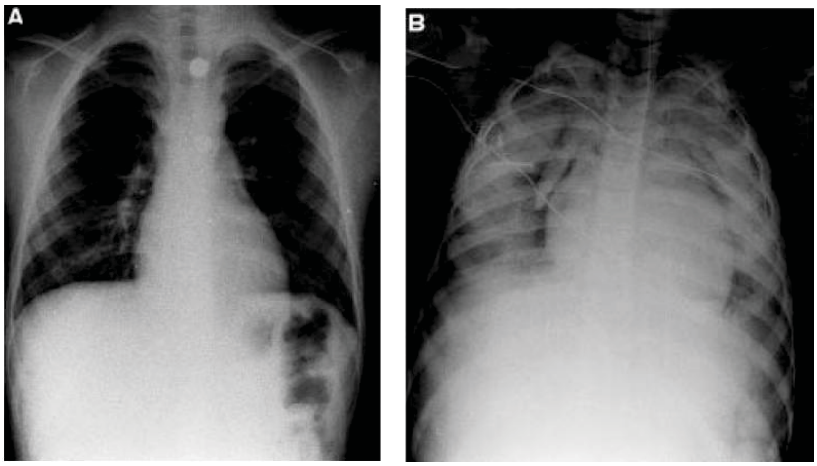


Figure 2. Human Nipah virus infections in Bangladesh, by month of illness onset, 2001–2007.

Gurley et al, 2007

Clinical features and risk factors of pulmonary oedema after enterovirus-71-related hand, foot, and mouth disease

Luan-Yin Chang, Tzou-Yien Lin, Kuang-Hung Hsu, Yhu-Chering Huang, Kuang-Lin Lin, Chuen Hsueh, Shin-Ru Shih, Hsiao-Chen Ning, Mao-Sheng Hwang, Huei-Shyoung Wang, Chin-Yun Lee



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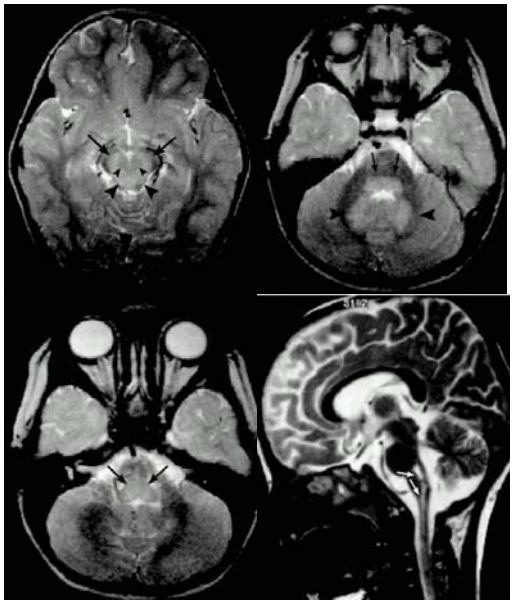
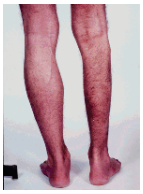
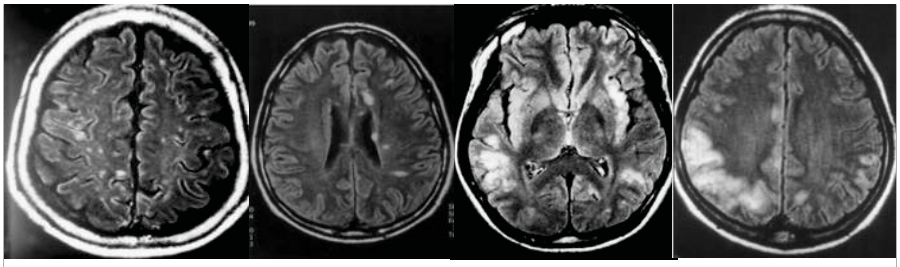




Enterovirus 71
Poliomyelitis-like
Brainstem encephalitis
with neurogenic
pulmonary edema
SAME VIRUS WITH DIFFERENT CLINICAL MANIFESTATIONS
1969 - discovered
1975 - Bulgaria (44)
1978 - Hungary (47)
1997 - Malaysia
1998 - Taiwan
100,000 hand foot mouth
encephalitis 78/400

Huang et al. NEJM 1999



Acute encephalitits

- Vasculitis
- Brainstem signs
- High mortality

- WongKT et al. / Tan CT et al. / Lim CC et al./ Chua KB. Malaysia
- Chadha MS et al. India
- Hsu VP, et al. /Luby SP, et al. Bangladesh.

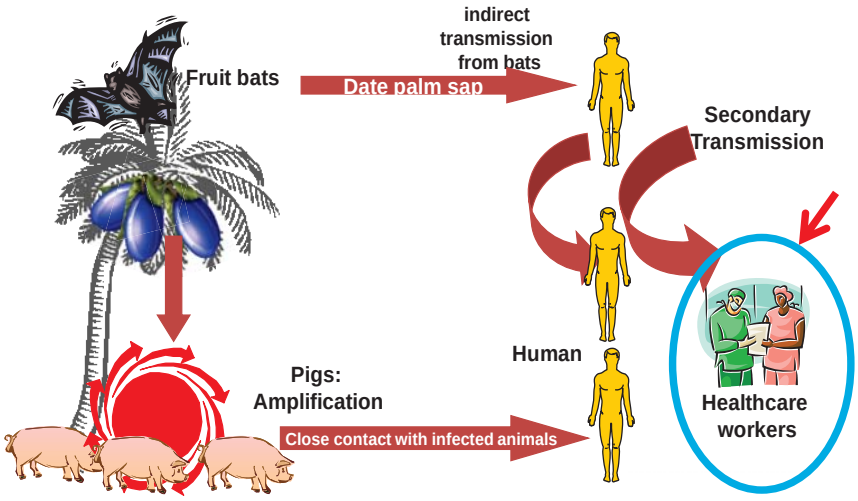
Late onset/relapse

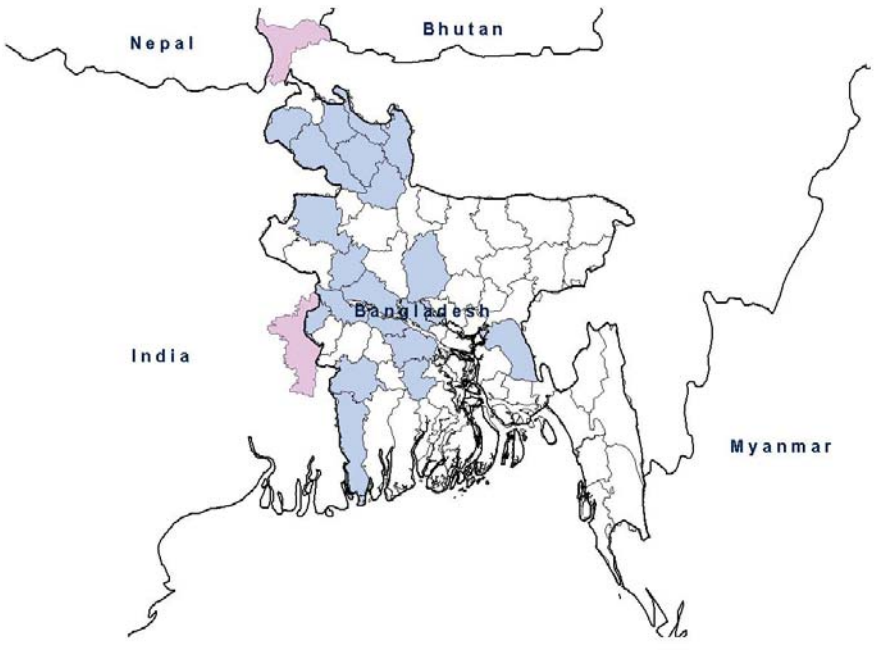
- Cortical involvement
- 3 - 4% non CNS (sub-clinical) had late onset
- 7 - 8% acute then relapse after 2 yrs.

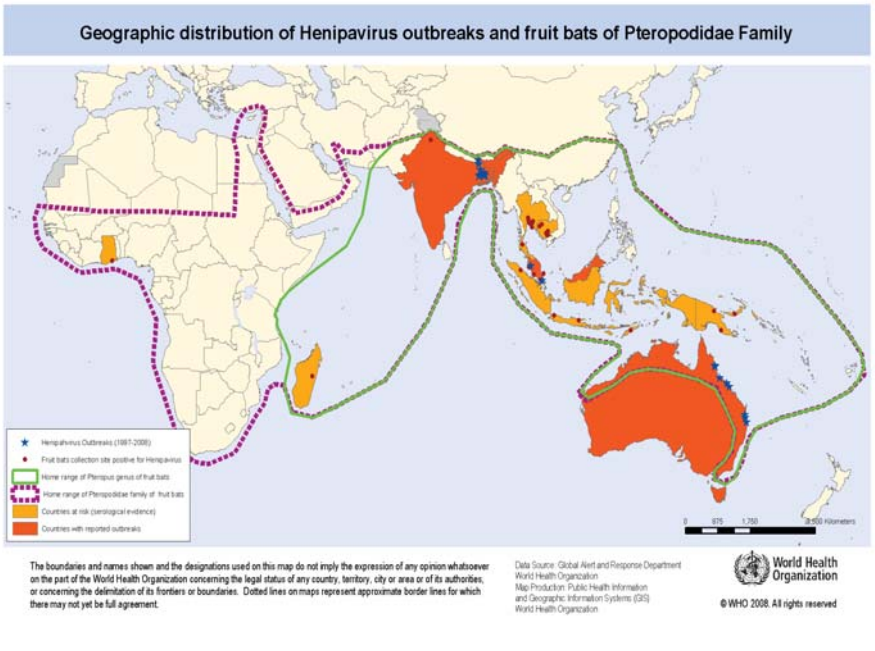
Table 3. Analysis of CSF specimens from 6 patients with laboratory-confirmed Nipah virus infection in 2004.

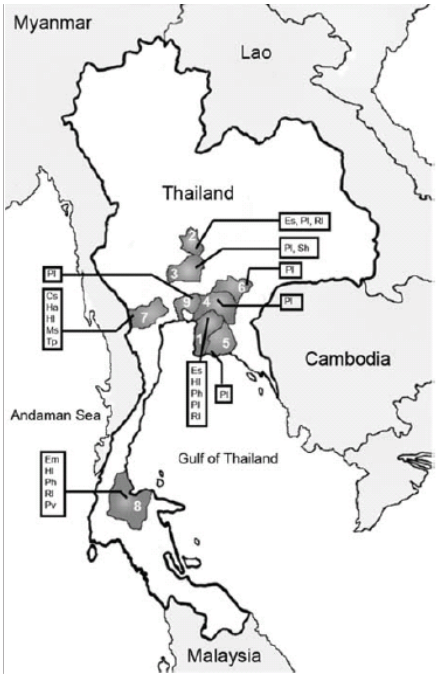
Patient	Age, years	WBC count, cells/mm³	RBC count, cells/mm³	Glucose level,[a] mmol/L	Protein level,[b] mg/dL	Culture result	Outcome
1	10[c]	1	2	…	…	No growth	Died
2	12	2	0	5.5	47	No growth	Survived
3	35[d]	4	3	3.3	30	No growth	Survived
4	26	5	0	4.3	58	Not done	Died
5	10[e]	9	27	4.8	64	No growth	Survived
6	18[f]	2500	Moderate	3.8	181	No growth	Died

Nipah virus transmission









Bat Nipah Virus, Thailand

Supaporn Wacharapluesadee,* Boonlert Lumlertdacha,† Kalyanee Boongird,‡ Sawai Wanghongsa,‡ Lawan Chanhome,† Pierre Rollin,§ Patrick Stockton,§ Charles E. Rupprecht,§ Thomas G. Ksiazek,§ and Thiravat Hemachudha*

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 12, December 2005

Figure. Locations in Thailand where bats have been captured. 1 = Chon Buri, 2 = Sing Buri, 3 = Ayutthaya, 4 = Cha Choeng Sao, 5 = Ra Yong, 6 = Pra Chin Buri, 7 = Ratcha Buri, 8 = Surat Thani, 9 = Bangkok. Species analyzed: Cs = *Cynopterus sphinx*, Em=*Emballonura monticola*, Es = *Eonycteris spelaea*, Ha = *Hipposideros armiger*, Hl = *Hipposideros larvatus*, Ms = *Megaderma spasma*, Ph = *Pteropus hypomelanus*, Pl = *P. lylei*, Pv = *P. vampyrus*, Rs = *Rousettus leschenaulti*, Sh = *Scotophilus heathi*, Tp = *Tadarida plicata*.

Table. ELISA, PCR saliva, and PCR urine results for Nipah virus from 12 bat species, Thailand, 2002–2004*

		ELISA		PCR saliva‡		PCR urine‡	
Species	Total bats	No. analyzed	No. positive (%) †	No. analyzed	No. pool positive/total	No. analyzed	No. pool positive/total
Frugivorous							
Cynopterus sphinx	34	10	0	34	0/5	34	0/5
Eonycteris spelaea	64	54	0	64	0/7	64	0/7
Pteropus hypomelanus	36	26	4 (15.4)	36	0/6	35	0/6
P. lylei	857	813	76 (9.3)	845	1/87	845	6/87
P. vampyrus	39	39	1 (2.6)	39	0/4	39	0/4
Rousettus leschenaulti	11	4	0	6	0/3	6	0/3
Insectivorous							
Emballonura monticola	14	12	0	14	0/2	14	0/2
Hipposideros armiger	88	6	0	88	0/10	88	0/10
H. larvatus	95	74	1 (1.3)	94	1/10	91	0/10
Megaderma spasma	13	0	0	13	0/2	13	0/2
Scotophilus heathi	3	3	0	3	0/1	3	0/1
Tadarida plicata	50	13	0	50	0/5	50	0/5
Total	1,304	1,054	82 (7.8)	1,286	2/142	1,282	6/142

*ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.
†ELISA positive: titer ≥1:400.
‡10 individual samples (saliva or urine) from the same species, colony, and the time of capture were saved into the same pool.

Drinking Bat Blood May Be Hazardous to Your Health

Supaporn Wacharapluesadee,[1]
Kalyanee Boongird,[2] Sawai Wanghongsa,[2]
Patta Phumesin,[1] and Thiravat Hemachudha[1]

[1]Molecular Biology Laboratory for Neurological Diseases, Chulalongkorn University Hospital, and [2]Ministry of Natural Resources and Environment, Bangkok, Thailand

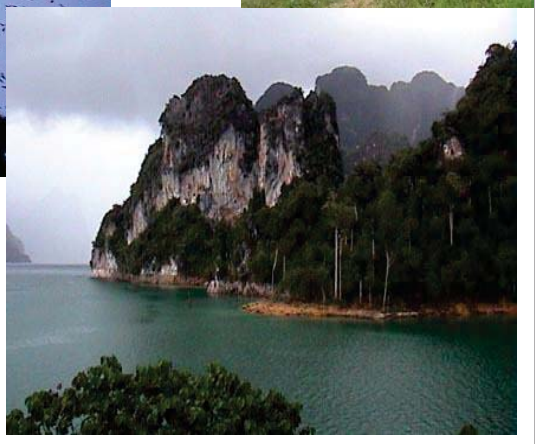
Clinical Infectious Diseases 2006; 43:268–9

bat specimen collection



blood sali□a □rine





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Seasonal preference of transmission
April – May – June

VECTOR-BORNE AND ZOONOTIC DISEASES
Volume 00, Number 00, 2009
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DOI: 10.1089/vbz.2008.0105

A Longitudinal Study of the Prevalence of Nipah Virus in *Pteropus lylei* Bats in Thailand: Evidence for Seasonal Preference in Disease Transmission

Supaporn Wacharapluesadee,[1] Kalyanee Boongird,[2] Sawai Wanghongsa,[2] Nitipon Ratanasetyuth,[1] Pompun Supavonwong,[1] Detchat Saengsen,[2] G.N. Gongal,[3] and Thiravat Hemachudha[1]

BRAIN MAPPING HUMAN ENCEPHALITIS

TARGET = 300/3 YEARS (2011-2013)
PROTOCOL POSTED ON WEB BY 2013
(NORMAL CONTROLS 400-500)

DEVELOPMENT OF LAB PLATFORMS WITH AFRIMS

(ARCHIVED/NEWLY ACQUIRED SAMPLES)

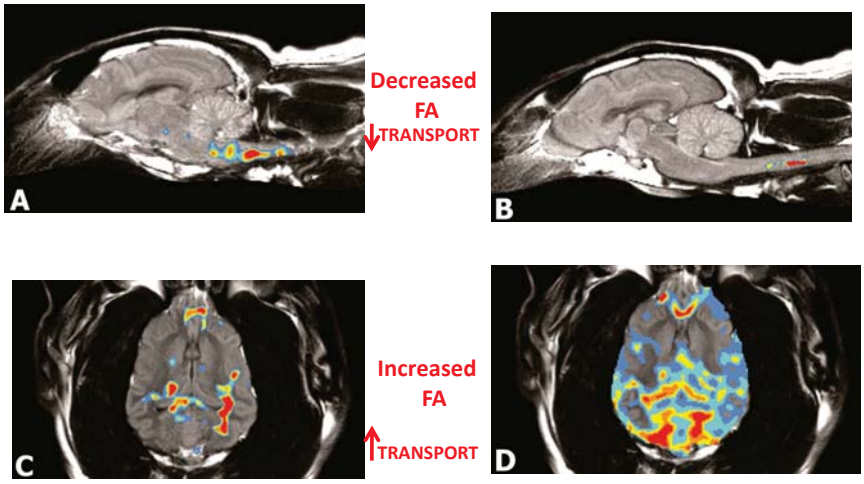
HUMANS WITH AES, ILI

SWINE, BATS

PLATE ARRAY (133 VIRUSES)
GENERIC PRIMERS FOR VIRAL FAMILIES
MASS TAG
NGS 454 ION TORRENTS ILLUMINA

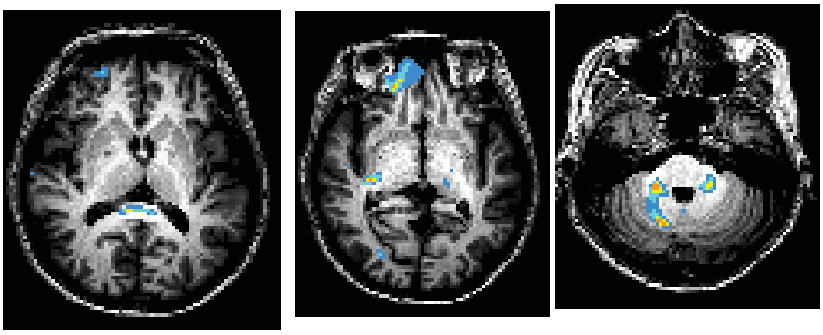
THAI GOVERNMENT FUND
AND GRANT FROM US ARMY RESEARCH LABORATORY (DOD)

paralytic furious



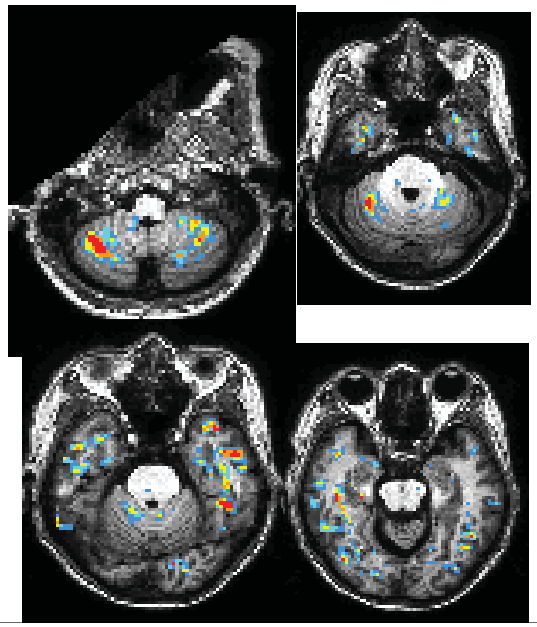
Demonstration best visualized by diffusion tensor imaging (Fractional Anisotropy)
Laothamatas, Sungkarat, Hemachudha. Adv Viral Res 2011

DECREASED FA (FRACTIONAL ANISOTROPY) – DIMINISHED TRACT INTEGRITY



26 year-old male, fever, headache, confusion for 4 days. Examination revealed extrapyramidal signs. MRI was normal

28 year old. Fever 1 month, psychosis 2 weeks



Increase MD
(mean diffusivity) = BBB leakage

Zoonotic disease

- It is real
- Many undiagnosed cases linked to animals
- Encephalitis – bigger problem than expected