



HK-3: Case Sharing on Clinical Management of Neurological Zoonotic Diseases

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Cryptic Case

A Pain in the Leg

History

- 39 woman presented to small district general hospital near Liverpool, UK
- 4 days Left Leg Pain
 - Started lower back radiating to leg
 - Severe, shooting, getting worse
 - Headache, vomited once
- 4 months Intermittent diarrhoea
 - Started 2 weeks before a trip to India
 - Dodgy mushrooms, puppy nip
 - Flexible sigmoidoscopy, gastroscopy normal
- Past History, Functional Enquiry, Family History
 - unremarkable

On examination

- Temp 38.5°C
- Very painful left leg,
 - weak, flaccid areflexic
 - sensory loss L4-S1 dermatomes
- Rest of examination unremarkable

What do you think is the most likely diagnosis?

What do you think is the most likely diagnosis?

1. Prolapsed disc
2. Spinal abscess
3. Guillain-Barré syndrome
4. Polio
5. Other

Investigations, Treatment, Progress

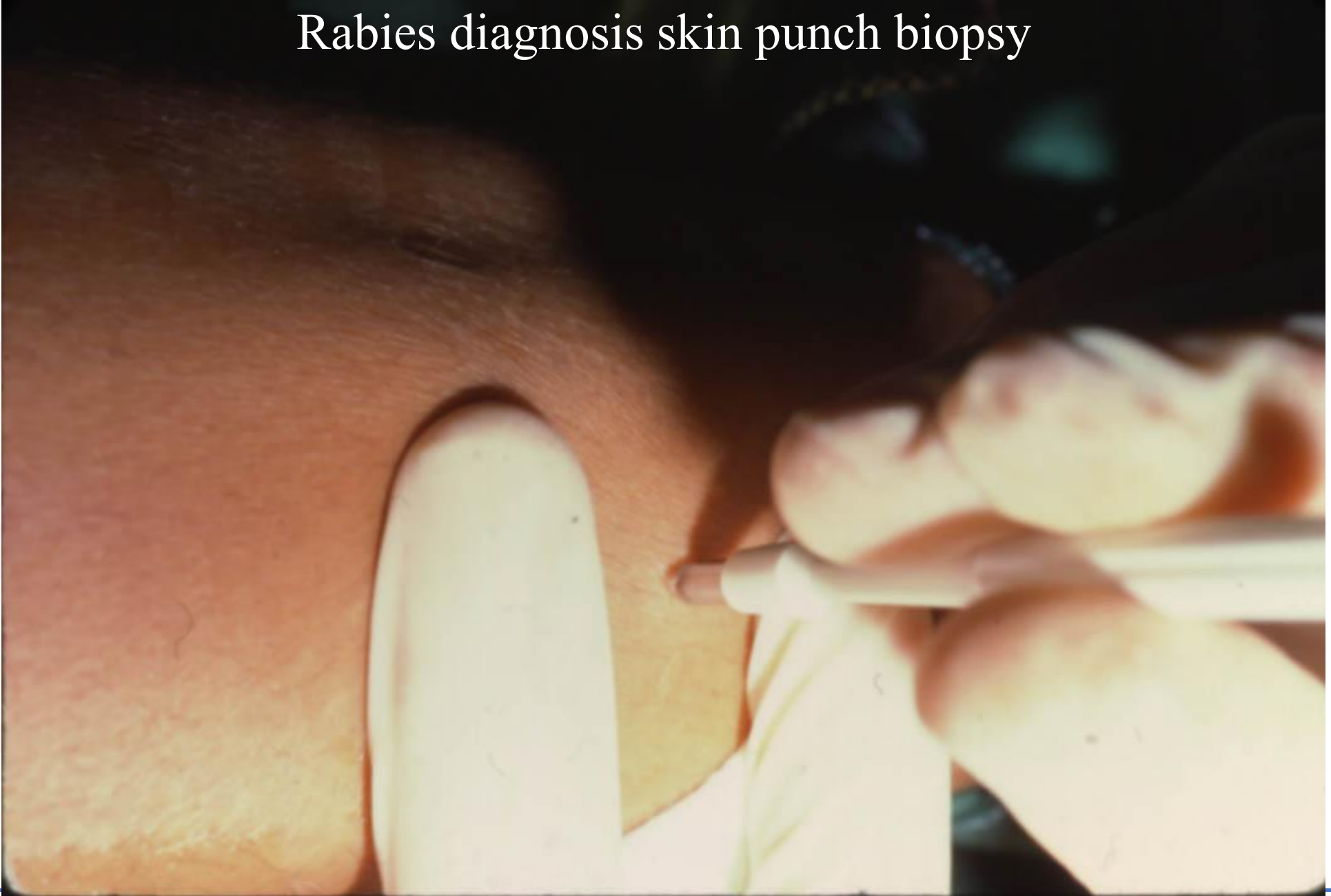
- Morphine for pain
- CT scan spine → no disc disease
- Progress
 - sore throat, difficulty swallowing, swollen left eyelid, goose pimple rash on skin, bilateral hearing loss
- Day 8 referred medical team,
 - now lethargic, flaccid weakness in both legs and arms.
 - provisional diagnosis of Guillain- Barré syndrome
 - treated with intravenous immunoglobulin

- Lumbar puncture
 - clear cerebrospinal fluid
 - white cell count 11 cells/l
 - 9 lymphocytes, 2 polymorphonuclear
 - red cell count of 4 cells/l,
 - protein 2.16 g/dL,
 - glucose 3.1 mmol/l, (plasma 5.9 mmol/l)

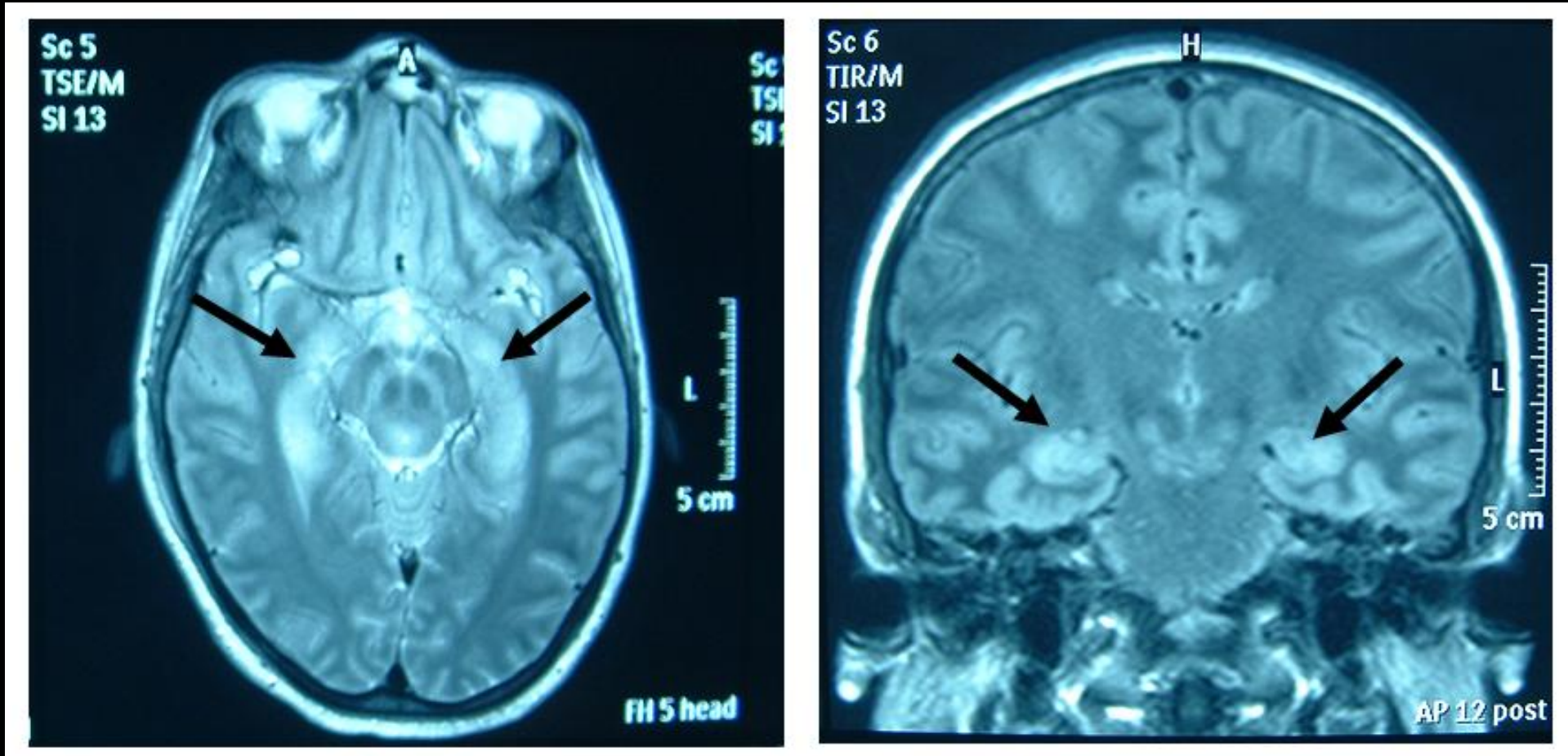
- Day 11 increased drowsiness; intubated ventilated.
- Day 13 she had absent oculoccephalic reflexes, and unreactive pupils,
- Computed tomography scan brain normal.
- Day 15 contacted Neurology Centre for advice

- Diagnosis
 - ? **Paralytic rabies (ascending paralysis, history of dog bite in India)**
 - ? Miller Fisher syndrome
 - ? Bickerstaff encephalitis
 - ? Other
- Action
 - Saliva, serum, skin biopsy for rabies
 - Hemi-nested reverse transcriptase PCR nucleoprotein
 - Real time PCR
 - *Smith et al J Med Virol 2003*
 - Barrier nursing / isolation
 - Transfer to Neurology Centre
 - Confirm Diagnosis
 - Experimental therapy for Rabies

Rabies diagnosis skin punch biopsy

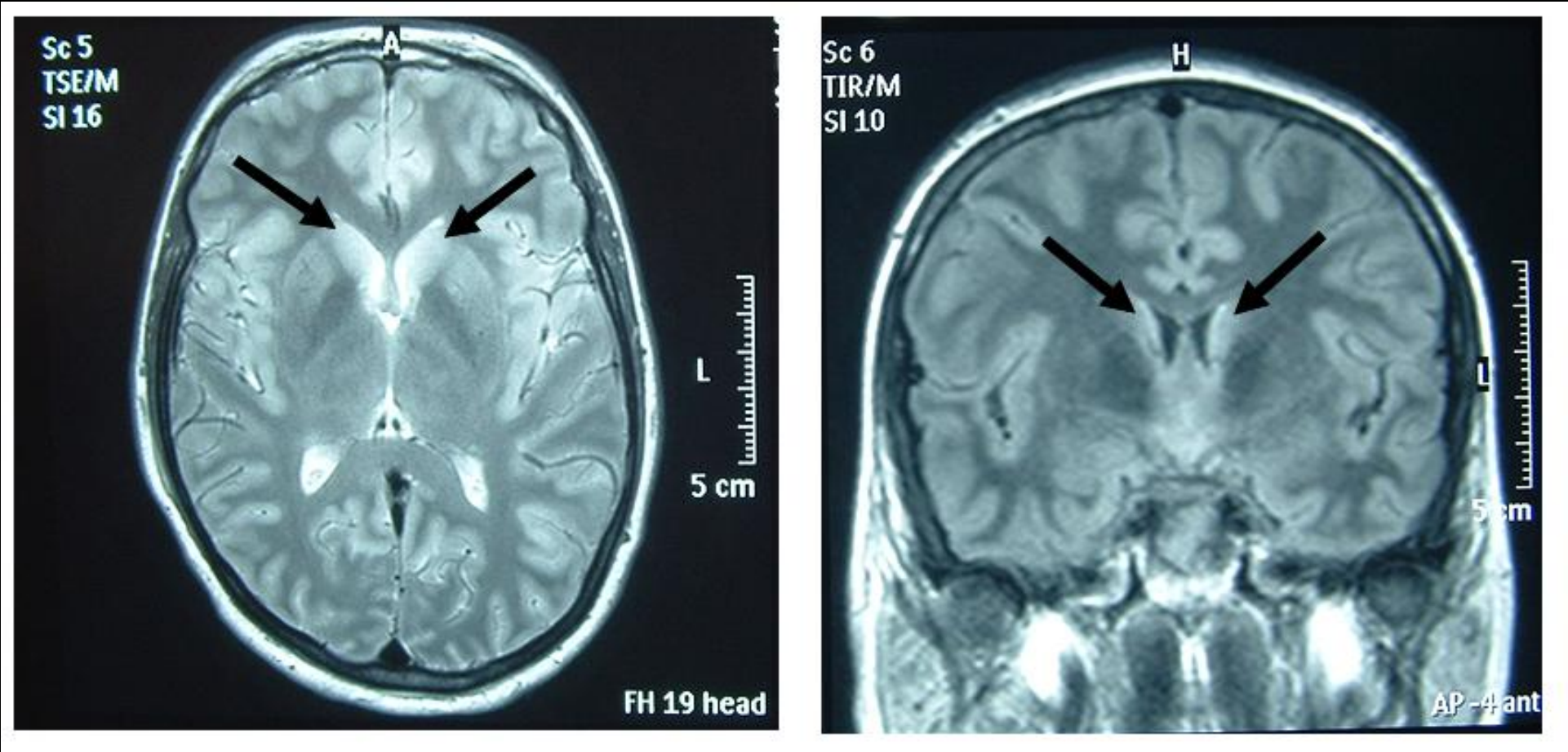


T2-weighted magnetic resonance imaging

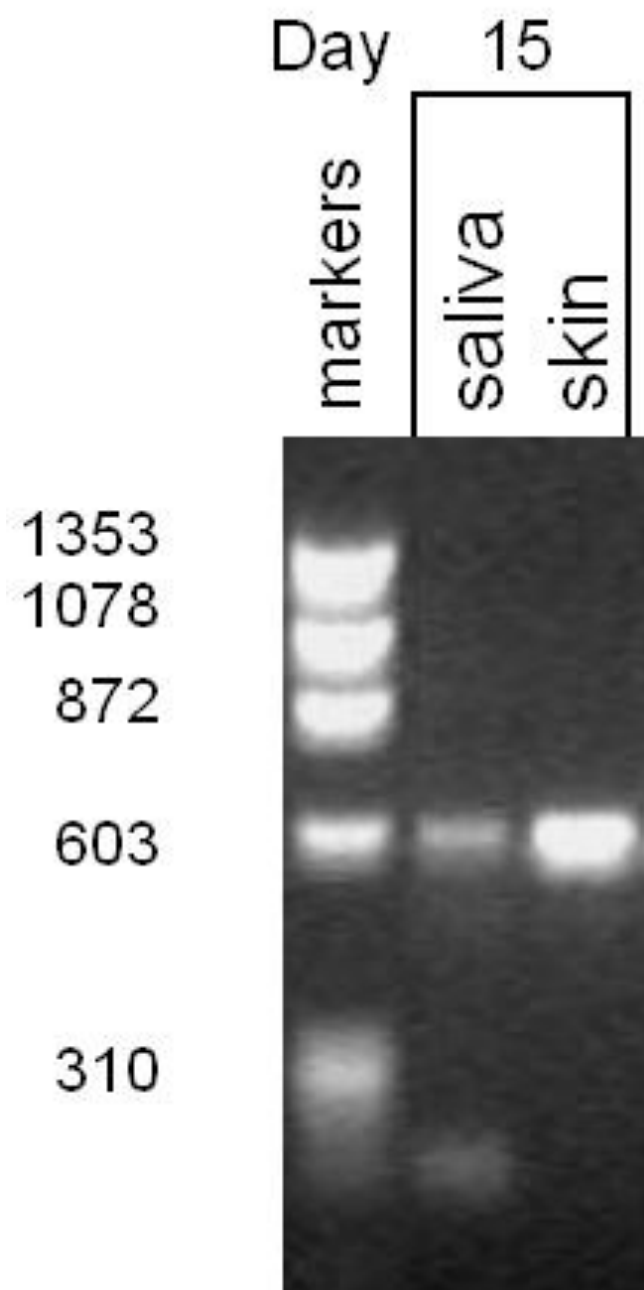


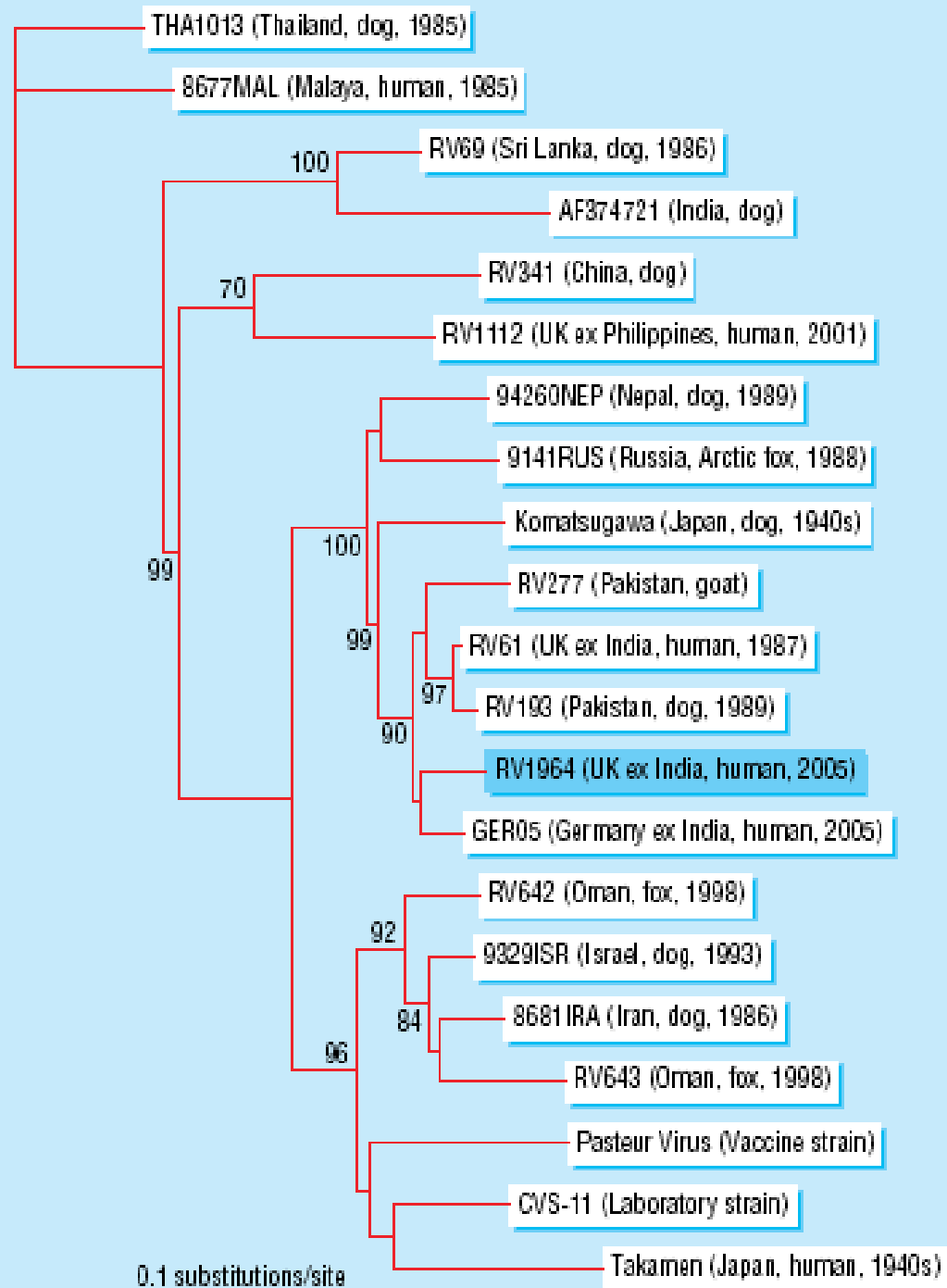
(Left: Axial View – T2 Turbo Spin Echo; Right – Coronal View T2 Fluid-attenuated inversion recovery – FLAIR).

T2-weighted magnetic resonance imaging



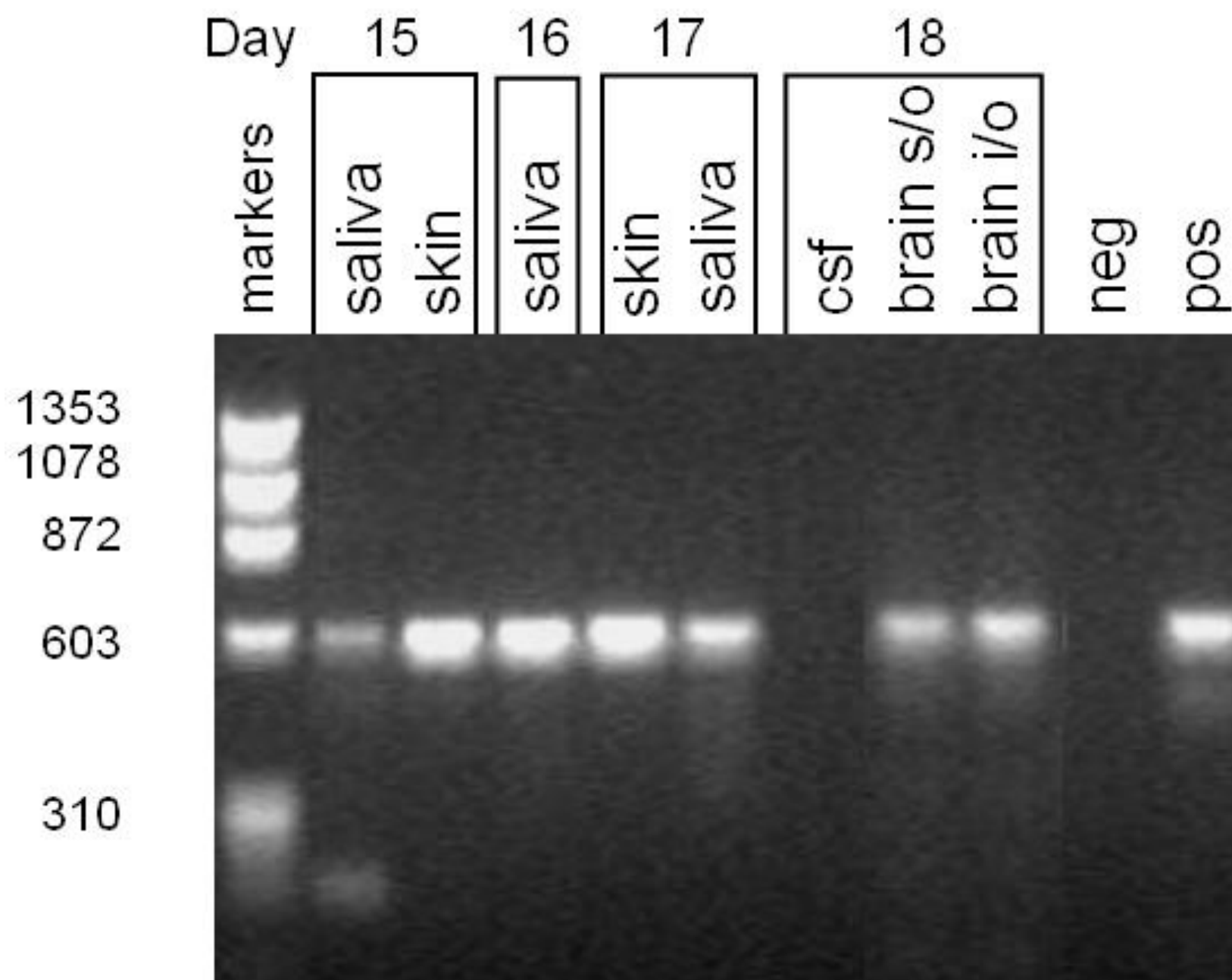
(Left: Axial View – T2 Turbo Spin Echo; Right – Coronal View T2 Fluid-attenuated inversion recovery – FLAIR).



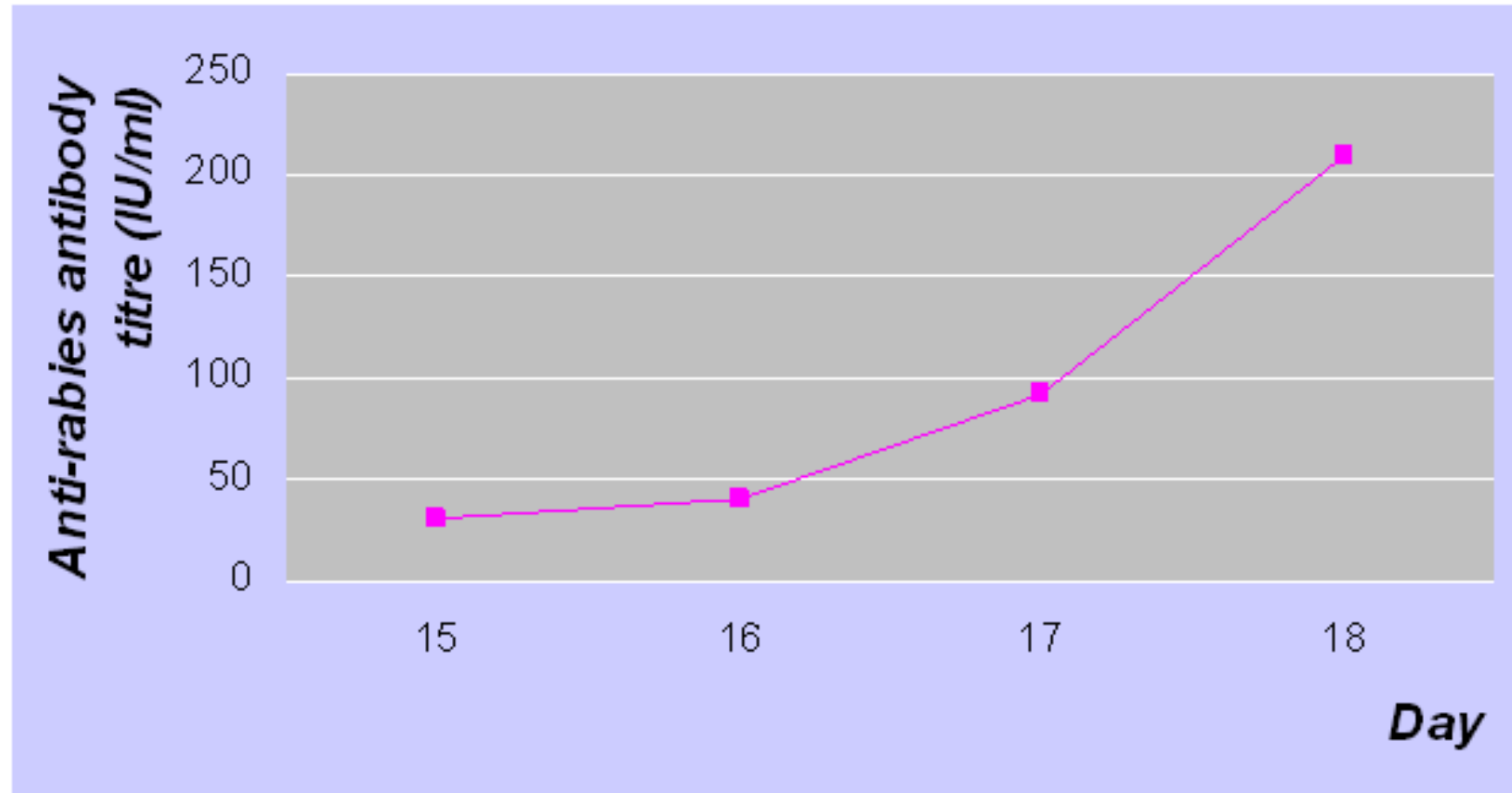


- Phylogenetic tree of 400 base pair region of nucleoprotein

- PCR diagnosis confirmed
- Too sick for experimental antiviral treatment
- Ionotropic support was withdrawn
- Patient died on the 18th day of admission.
 - never had hydrophobia, aerophobia (fear of air), hypersalivation, or spasms.
- Post-mortem needle biopsy
 - foramen magnum and supraorbital routes;
 - Rabies confirmed by fluorescent antibody testing and PCR.



Fluorescent virus neutralisation assay



Last Updated: Friday, 22 July, 2005, 11:49 GMT 12:49 UK

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Rabies victim dies after holiday

A British woman has died after contracting rabies on holiday in the popular Asia tourist destination, Goa.

Health officials said the woman, who is in her 30s and from Bury in Greater Manchester, was admitted to Fairfield General Hospital.

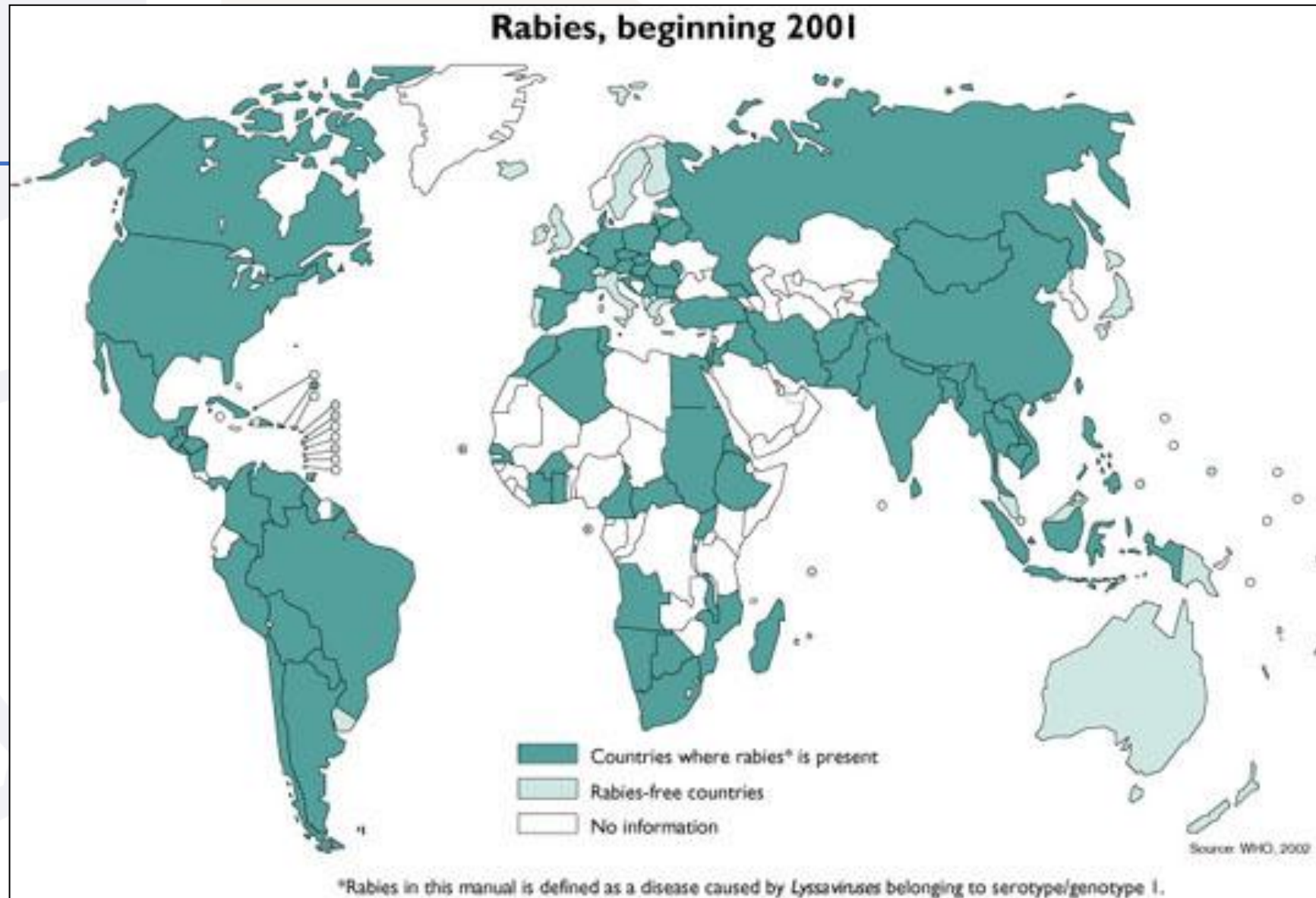


She was transferred to the Walton Centre for Neurology and Neurosurgery, Liverpool, where she died on Saturday.

The Health Protection Agency North West said hospital staff were offered rabies vaccines as a "precautionary measure".

Rabies

- Rabies Epidemiology
- Rabies Clinically
- Prevention of Rabies



Approx 40,000 cases annually

Man dies from rabies after bat bite in Scotland



Sunday, 24 November,
2002, 21:59 GMT

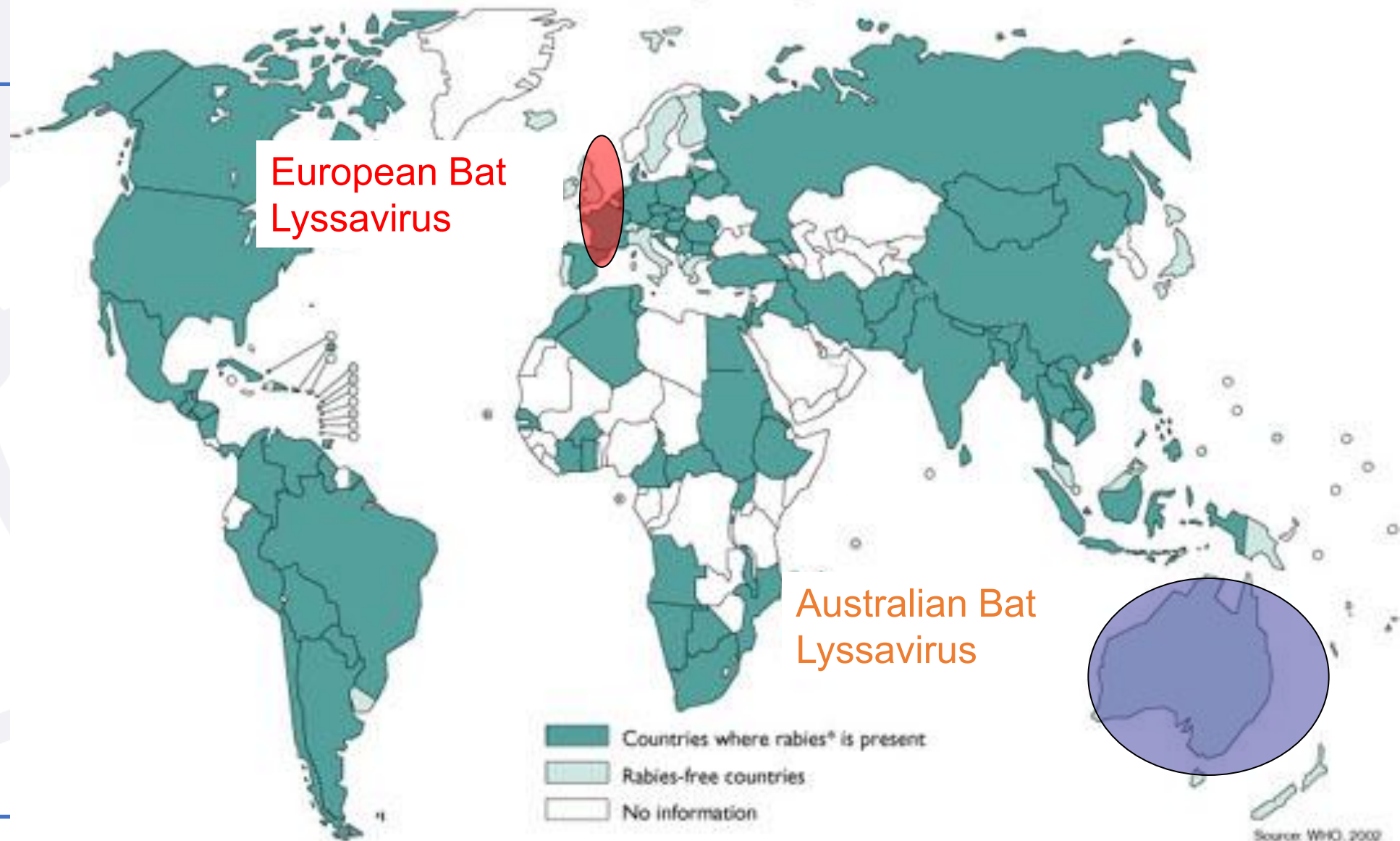
David McRae worked with bats as a conservationist

A man has died after contracting Britain's first case of rabies for 100 years, hospital bosses have confirmed.

David McRae, a 56-year-old conservationist from Guthrie, Angus, Scotland, failed to recover from European Bat Lyssavirus (EBL), a type of rabies found in several northern European countries.

Mr McRae, who was licensed to handle

Rabies, beginning 2001



*Rabies in this manual is defined as a disease caused by Lyssaviruses belonging to serotype/genotype 1.

Source: WHO, 2002

Daubenton's bat



Family *Rhabdoviridae*, genus *lyssavirus*

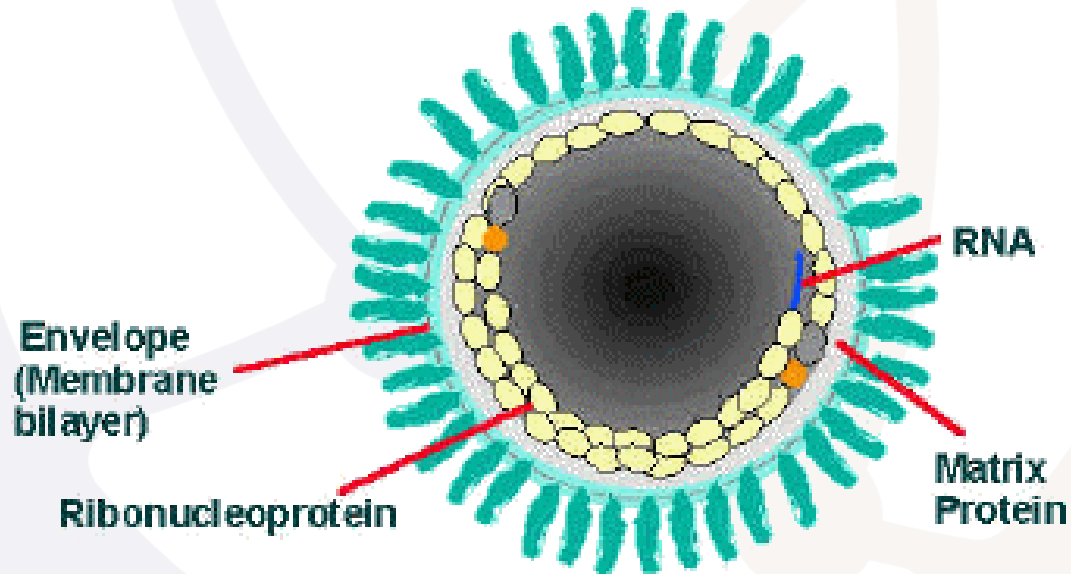
	GENOTYPE	SOURCE	DISTRIBUTION
1	Rabies virus	Dog, fox, raccoon, bat etc	Widespread
2	Lagos bat virus	Bats, cats,	Africa (rare)
3	Mokola virus	Shrews, cats	Africa
4	Duvenhage	Insectivorous bat	Africa
5	European bat Lyssavirus Type 1	Insectivorous bat	N & E Europe
6	European bat Lyssavirus Type 2	Insectivorous bat	W Europe
7	Australian bat Lyssavirus	Flying foxes Insectivorous bat	Australia (Philippines?)

Clinically all give “rabies” except
Lagos bat virus – no human disease,
Mokola virus – fever, encephalopathy

Virology

- Negative sense RNA
- Family *Rhabdoviridae*
- Genus *Lyssavirus*

Cross Sectional



Rabies epidemiology

- Natural cycle among
 - Insectivorous bats
 - do not always die
 - Up to 8% of some populations seropositive
 - Wild mammals (skunks, raccoons, foxes, insectivorous bats)
 - Domestic animals (dogs*, cats)

National Rabies Survey India, Annually:

- 20,000 deaths
 - 60% children
- 8 million exposures to dog bite
 - Half children
 - Half seek no advice or Rx (except herbal)

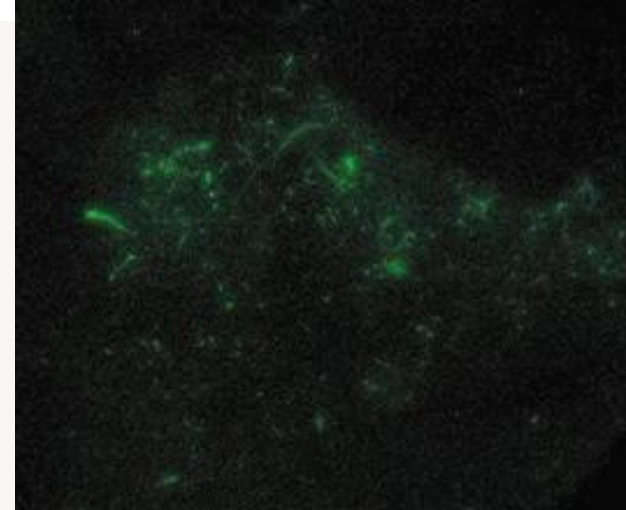


c/o Dr Madhusudana, NIMHANS, Bangalore

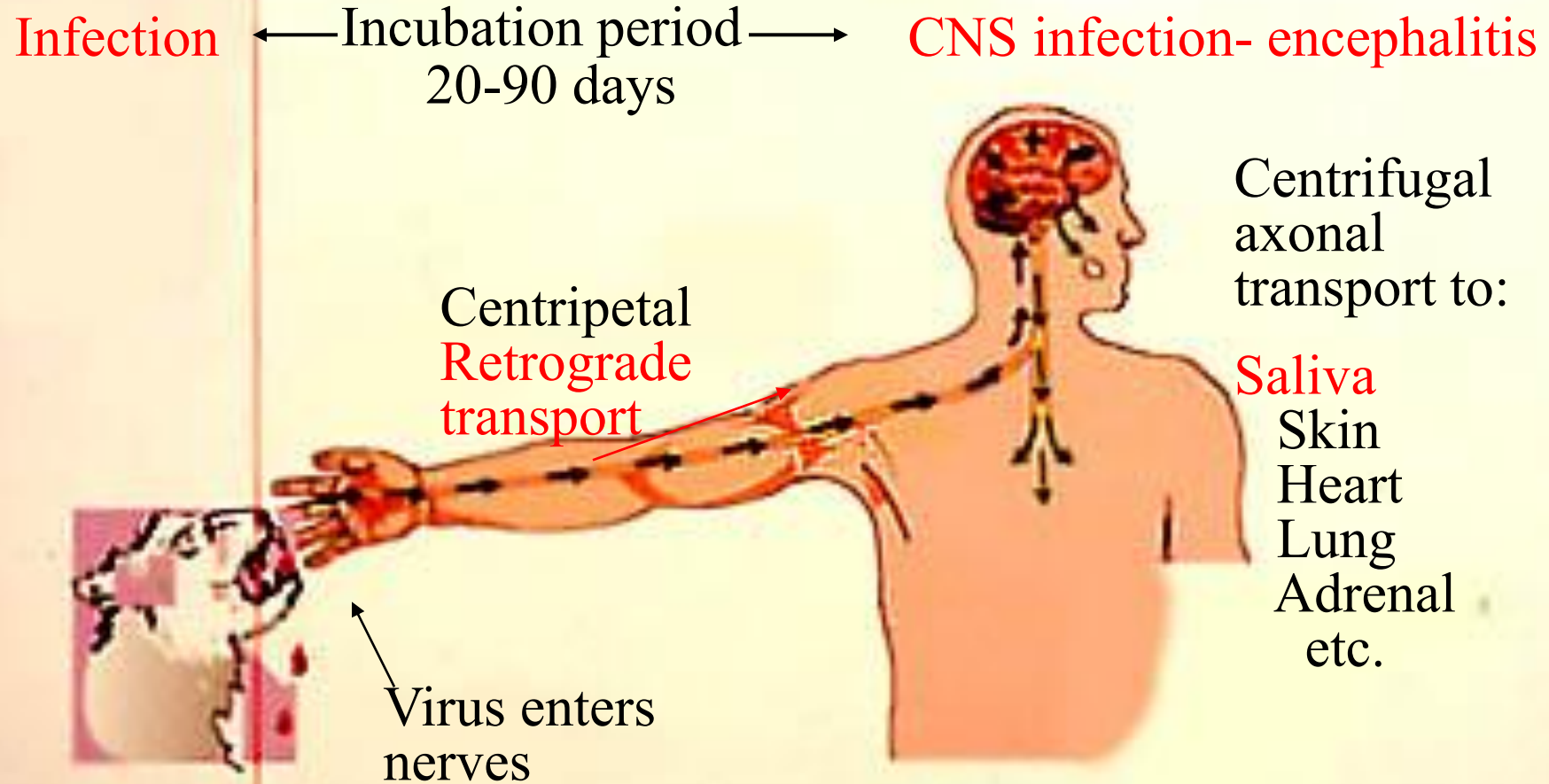
Rabies encephalitis in a Malaria-Endemic area, Malawi, Africa

- Rabies was responsible for 14 (10.5%) of 133 fatal cases of suspected CNS infection
- Four patients had unusual clinical manifestations
 - rabies was only diagnosed post mortem.
- Three (11.5%) of 26 fatal cases were originally attributed to cerebral malaria.

- Detection of rabies virus nucleoprotein with the fluorescent antibody test (FAT) in post-mortem brain material



Rabies pathogenesis



Inoculation

- Route of inoculation
 - Broken skin
 - Mucous membranes
 - Transplants
 - cornea
 - Other organs
 - (inhaled)
- Incubation period
 - 2-3 months
 - (days to years)

Early clinical features

- Skin itching, pain, paraesthesia in dermatome of inoculum (30-80%)
- Fever, insomnia, anxiety, headache



Hemachudha et al TLN 2003

Clinical features of FURIOUS rabies (70%)

- Encephalopathy
 - Confusion, agitation, aggression
 - Phases of arousal and lucid intervals
- Autonomic stimulation:
 - excess salivation, frothing
 - temp control
 - priapism
- Spasms, hydrophobia, aerophobia
- Cranial nerve lesions III, VII, VIII
- Paralysis
- Coma

Furious rabies: differential diagnosis

Furious rabies: differential diagnosis

- Hysterical pseudo-hydrophobia
- (Cephalic) tetanus
- Other brain stem encephalitides
 - Enterovirus, borrelia, brucella, mycoplasma
- Other causes of muscle spasms
 - (eg phenothiazine dystonia, tetany, strychnine poisoning)
- Delirium tremens
- Cerebrovascular accident, epilepsy
- Porphyria

PARALYTIC 'dumb' RABIES

- Accounts for 30% of rabies
- Ascending paralysis, loss of tendon reflexes
- Fasciculation
- Sphincter dysfunction
- Fever, sweating, gooseflesh
- Bulbar / respiratory paralysis
- (hydrophobia)
- Survive < 30 days

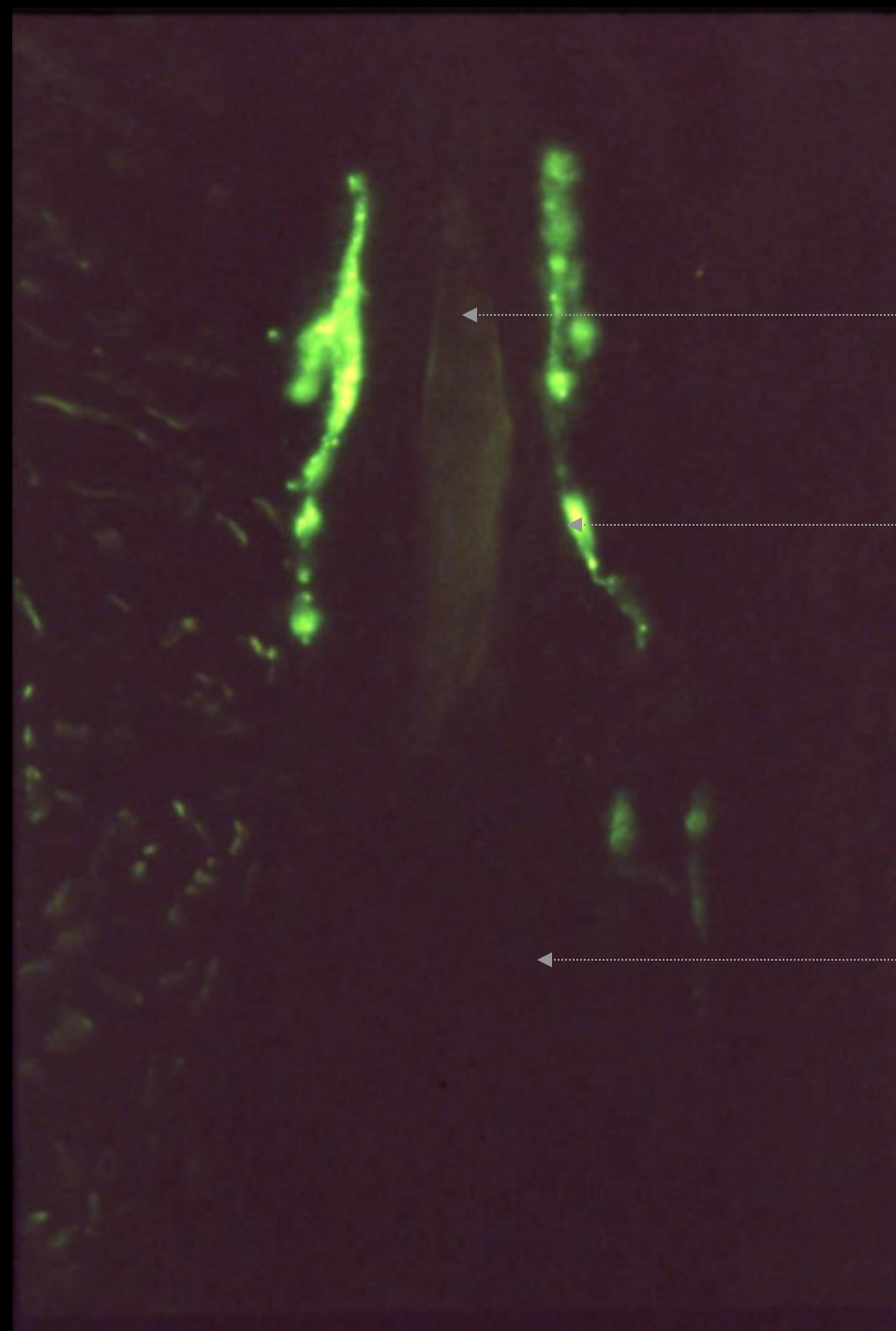
Paralytic rabies: differential diagnosis

- Post-vaccinal encephalomyelitis
- Paralytic poliomyelitis
 - Other enteroviruses
- Flavivirus myelitis
- Other causes of acute ascending paralysis (eg– Guillain-Barré syndrome)
- *Herpes simiae* (B virus) encephalomyelitis (after monkey bites)
- *So provide full Rx, until diagnosis of rabies made*

Diagnosis

- Usually clinical diagnosis
- Skin biopsies – PCR (or antigen detection)
- Saliva / Tears - PCR
- Serum – antibody detection
- CSF PCR, Antibody detection
- Repeat samples daily until diagnosis made

Rabies diagnosis
vertical skin
biopsy



Hair

Rabies antigen

Base of hair
follicle

MJ Warrell

Treatment of established rabies

See Jackson et al Clin ID 2003

- Industrial doses of sedatives
 - Diazepam
 - Chlorpromazine
 - Diamorphine

“Lie through your teeth about the diagnosis”

Barrier nursing, saliva theoretically infectious, but no cases documented

Vaccination of exposed staff

Vaccination of intimate contacts

Inform Public Health Authorities

Recovery from Rabies?

- 5 well-documented cases of survival in patients that had received some vaccination but developed clinical disease,
 - 6 year old bitten by bat, rabies Abs in CSF & serum; Rx with post exposure duck embryo vaccine
 - Argentine woman, bitten by dog, serological diagnosis, post exposure duck embryo vaccine
 - 1977 previously vaccinated microbiologist, inhaled rabies virus, partial recovery

All had severe sequelae

Treatment successes or failures of vaccination regimen?

- Rabies 100% fatal if no vaccination and clinical disease develops...

Treatment for Rabies?

- Teenage girl in Wisconsin
- Bitten by bat, no vaccination, subsequently developed features of paralytic rabies
 - Evidence for rabies – antibody only, no virus isolate, no PCR (ie could it have been another lyssavirus)
- Treated with
 - Ketamine (anti-excitotoxic NMDA receptor antagonist, anti-viral)
 - Benzodiazepines
 - Amantadine
 - Ribavirin
- Survived with moderate sequelae
 - Back to school

JEANNA GIESE

RABIES SURVIVOR

HOME PAGE MY STORY RABIES INFO GUESTBOOK
CONTACT JEANNA

<http://www.youtube.com/watch?v=VT7yoyKbYu0>



MY STORY

I am Catholic. On Sunday September 12, 2004, I attended mass with my mother at St. Pat's Church in Fond du Lac, WI.

About 15 minutes from the end of mass, a little bat started flying around the church and bothering the congregation. The bat flew to the back of the church and an usher hit it to the floor and left it where it fell on the top of the steps.

Being the animal lover that I was, and still am today, I walked back to the bat with the intention of releasing it outside. When I reached the bat, I quickly noticed how cute it was and assessed the situation: the bat was on its stomach with its back towards me.

I crouched down and decided that the safest way to pick it up would be by the tips of the wings, so I did so. As soon as I grabbed the bat, it let out a very loud screech, and kept doing it, so I straightened up and turned outside. I reached the door and pushed it open with my hip.

As soon as I stepped outside, the Silver-haired Bat stretched over and sank its top left fang into my left index finger. THAT HURT. Like a needle injecting acid into your finger tip.

I walked over to a nearby pine tree and let

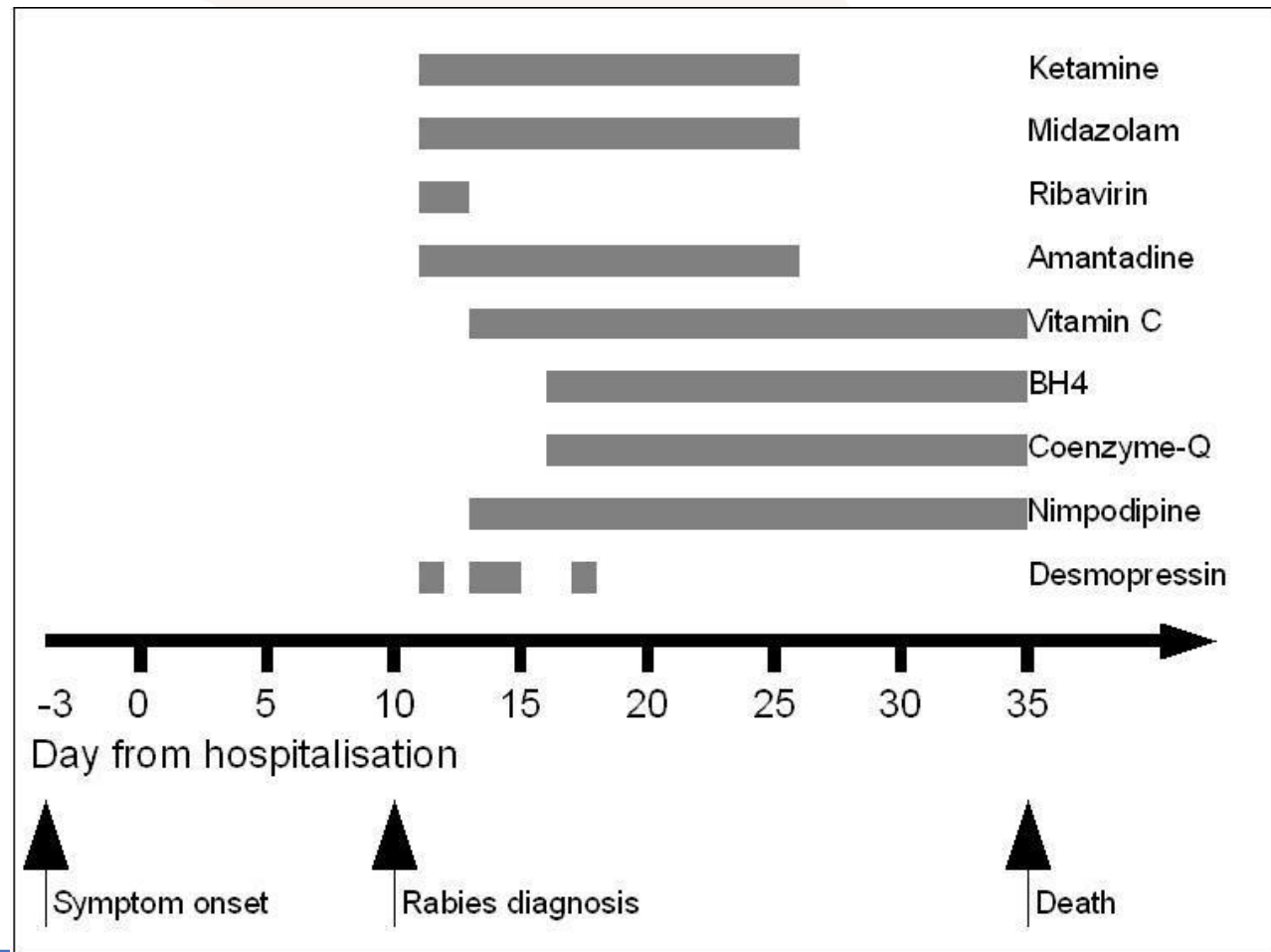


My pediatrician, Dr. Howard Dhoneau, came into my room Monday morning to check on me. my mom suddenly told him about the bat bite. He immediately rushed out of the room and called down to Children's Hospital of Milwaukee and told them that I am a possible rabies case.

I was sent down to Children's Hospital that Monday, October 16, 2004. When I arrived, they tested a skin sample from the back of my head and sent it to the CDC in Georgia. Rabies was confirmed, and I had less than 4 hours left to live.

Dr. Rodney Willoughby was not ready to let me die

- 37 year old woman presented with rabies in Northern Ireland
- visit to a monkey sanctuary in Limpopo province, South Africa, 24 months prior to admission, when she separated two fighting dogs. One of these dogs allegedly died of rabies.
- Visit to the South African monkey sanctuary, 9 months previously, she was bitten by a monkey.



Hunter et al. J Med Virol 2010



Case	Location	Genotype/source	Rabies antibodies	Rabies virus	Rabies antigens	Clinical outcome	Autopsy findings
Willoughby et al. [2005]	Milwaukee, US	Genotype 1/bat	Ab present at clinical presentation	No virus isolated	No viral antigens detected (2 skin biopsies and 9 saliva samples)	Survival	Not applicable
US Centers for Disease Control and Prevention [2007]	Indiana, US	Genotype 1/bat	Ab present at clinical presentation	RT-PCR positive for rabies virus (skin and saliva)	Skin and saliva positive via direct fluorescent antibody (DFA)	Deceased, 34 days after symptom onset	Rabies virus antigen detected in brain tissue at post-mortem
US Centers for Disease Control and Prevention [2007]	California, US	Genotype 1/bat	Negative at presentation. Became positive on day 12	RT-PCR positive for rabies virus (saliva)	Rabies virus antigens detected by corneal impressions (DFA)	Deceased, 29 days after symptom onset	Rabies virus antigen detected in brain tissue at post-mortem
Hemachudha et al. [2006]	Thailand	Genotype 1/dog	No antibody detected during clinical course	NASBA detected rabies RNA (hair follicle)	No comment	Deceased, 8 days after symptom onset	Rabies virus was isolated from brain and spinal cord tissues at necroscopy
Unpublished [2006]	Texas, US	Genotype 1/bat	Not known	Not known	Not known	Deceased ~7 days post-hospitalization	Not known
Schmiedel et al. [2007]	Germany	Genotype 1/dog	Ab not detected at presentation. Serum Ab response from day 11	RT-PCR positive for rabies RNA (saliva and corneal swab)	No comment	Deceased, 31 days after symptom onset	Autopsy performed "further virological investigations ongoing"
McDermid et al. [2008]	Canada	Genotype 1/bat	"Over time rabies IgG and IgM rose"	RT-PCR positive for rabies RNA (skin biopsy and saliva)	Rabies Ag detected by fluorescent antibody test	Deceased, 65 days after symptom onset	Rabies virus antigen detected at autopsy. Negri bodies present on pathology
Unpublished [2008]	Brazil	Genotype 1/bat	Antirabies antibody in blood and CSF. Increased over clinical course	RT-PCR identified virus RNA (skin follicle)	No comment	Survival	Not applicable
Unpublished [2008]	Germany (lung transplant recipient)	Genotype 1/dog	No neutralizing antibody response	RT-PCR detected rabies virus (CSF, sputum, BAL)	Virus isolated by cell culture	Deceased, 49 days post-transplant	Rabies RNA isolated from CNS tissue
Unpublished [2008]	Germany (kidney transplant recipient)	Genotype 1/dog	No neutralizing antibody response	RT-PCR detected rabies virus (CSF, saliva)	No virus cultured	Deceased, 52 days post-transplant	Rabies RNA isolated from CNS tissue
Unpublished [2008]	Germany (kidney and pancreas transplant recipient)	Genotype 1/dog		RT-PCR detected rabies virus (CSF, sputum, corneal swab)	Virus isolated by cell culture	Deceased, 95 days post-transplant	Rabies RNA isolated from CNS tissue
van Thiel et al. [2009]	Kenya	Genotype 4 (Duvenhage)/bat	Ab not detected (patient given HDCV d1, 4, 8, and 15)	RT-PCR detected DUVV (Nuchal skin biopsy and saliva)	No virus cultured	Deceased, 45 days post-incident with bat	Rabies virus antigen in frontal and temporal cortex, hippocampus and entorhinal cortex
Rubin et al. [2009]	Equatorial Guinea	Genotype 1/dog	Ab detected in serum d18 and CSF d20	RT-PCR detected rabies virus in Saliva	Rabies virus isolated from skin biopsy when inoculated into mice	Deceased. (NB death attributed to malnutrition and renal failure)	No comment
This case, 2008	Belfast, UK	Genotype 1/dog	Ab not detected at presentation. Serum and CSF Ab response from day 8	RT-PCR detected rabies virus (CSF, sputum, skin)	Virus isolated by cell culture	Deceased, 35 days after symptom onset	Rabies RNA isolated from CNS tissue. Viable rabies virus cultured. Antigen present.

Doesn't work!

Attempts to treat rabies with Milwaukee protocol – all failed



Case history 2

Case history

- A 43 year old man had been bitten by a dog 3 days earlier, and interrupted your morning coffee
- What questions would help you decide on a plan of action?
- And what action would you take?

If bitten – evaluate risk

1. Where is bite? Is skin intact?
2. Circumstances of bite
friendly play? Unprovoked?
3. Animal species
Its behavior/appearance/outcome
Vaccination Hx of animal
4. (Immunohistochemistry of animal brain)

If bitten - action

- CLEAN WOUND
 - ASAP
 - Soap/detergent
 - 10 mins
 - Debride dead tissue
 - *Don't suture*
 - Give tetanus





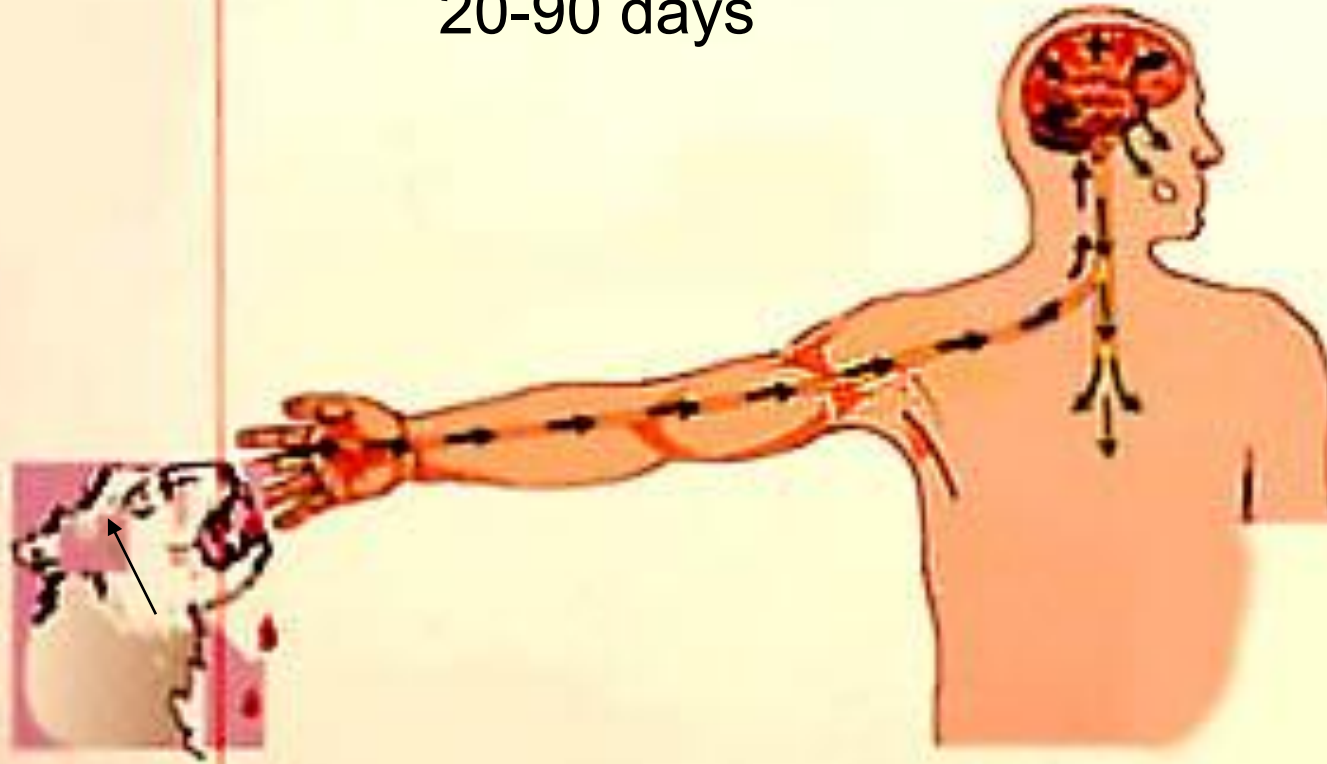
Vaccination against rabies

Pasteur 1880



Rabies pathogenesis and vaccination

Infection ← Incubation period 20-90 days → **Encephalitis**



Pre-exposure

Post-exposure

+/- Rabies
immunoglobulin (RIG)

If Started: 1st 24 hrs ----- when Symptomatic
Efficacy is: 100% ----- 0%

Categories of Rabies Exposure

Category I	Contact with animal, or licks on intact skin	No exposure
Category II	Nibbles on exposed skin Minor bite(s) or scratch(es) without bleeding	Minor exposure
Category III	Transdermal bite(s) or scratch(es) Licks on broken skin Contamination of mucous membranes by animal's saliva (licks) Direct contact with bats ¹	Severe exposure

Rabies Post Exposure Treatment Recommendations According to Category of Exposure

	Category I exposure –	Category II exposure –	Category III exposure –
	Immunologically naive individuals of all age groups		
	Washing of exposed skin surfaces.	Wound washing and immediate vaccination:	Wound washing and immediate vaccination:*
	No PEP required.	- 2-sites ID on days 0, 3 and 7 or - 1-site IM on days 0, 3, 7 and between day 14-18 or - 2-sites IM on days 0 and 1-site IM on days 7, 21	- 2-sites ID on days 0, 3 and 7 or - 1-site IM on days 0, 3, 7 and between day 14-18 or - 2-sites IM on days 0 and 1-site IM on days 7, 21
		RIG is not indicated.	RIG is recommended
	Previously immunized individuals of all age groups		
	Washing of exposed skin surfaces.	Wound washing and immediate vaccination*:	Wound washing and immediate vaccination*:
	No PEP required.	- 1-site ID on days 0 and 3 or - At 4-sites ID on day 0 or - At 1-site IM on days 0 and 3 –	- 1-site ID on days 0 and 3 or - At 4-sites ID on day 0 or - At 1-site IM on days 0 and 3 –
		RIG is not indicated.	RIG is not indicated.
Notes			

* Immediate vaccination is not recommended if complete PEP already received within <3 months previously.

ID: intradermal injection; IM: intramuscular injection; RIG: rabies immunoglobulins.

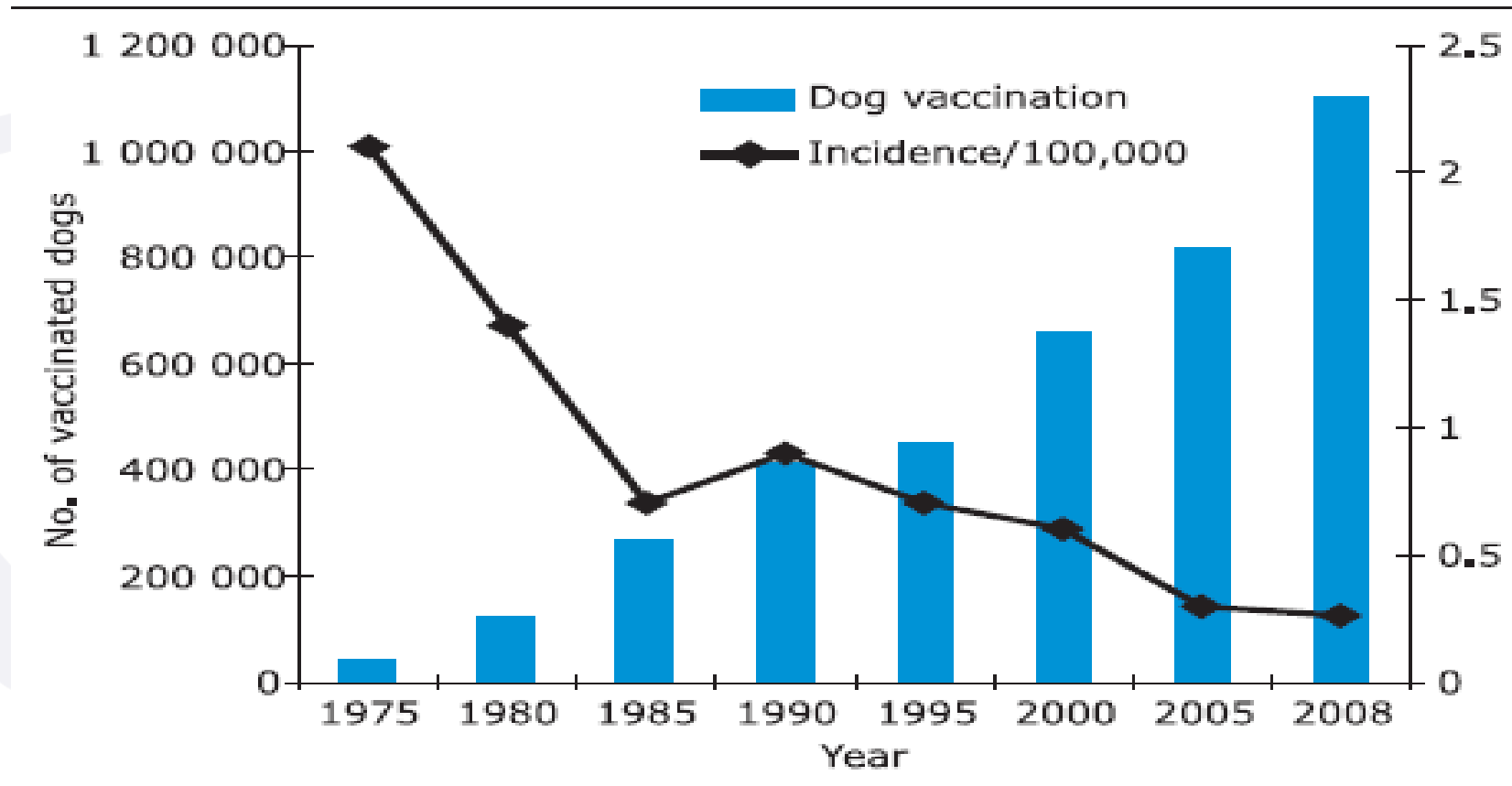
Avoiding bites

- “Rabid Dog”
- Lame Dog
- Dog with something “stuck in throat”
- Unusually tame wild animal
- Injured animal at roadside



Courtesy DW Warrell

Rabies Control: Impact of mass dog vaccination campaign on human rabies incidence, Sri Lanka, 1975-2005



liv.ac.uk/braininfections

twitter



@RunningMadProf

braininfectionsglobal.tghn.org