FAILED RABIES POST-EXPOSURE PROPHYLAXIS?

SPECIAL PATHOGENS UNIT, NICD
19 year old, previously healthy soldier

- **Category 3** exposure on finger - rabid yellow mongoose
- **13 hours**: wound toilet, human diploid cell vaccine IMI into gluteus, RIG (20IU/kg) 1ml into wound, rest into deltoid
- **Vaccine course**: days 3, 7, 14
- **Day 21**: onset of rabies-like illness, neg rabies Ag on saliva and CSF, rabies IgM 1:8 in serum (IFA)
- **Day 37**: died, serum rabies IgM 1:256 (IFA), rabies virus isolated from brain
- Shill NEJM
Reasons for failure of PEP?

- Vaccine and RIG potency adequate
- Cold chain maintained
- **Possible causes of failure:** administration of vaccine into the gluteus muscle, inadequate local wound administration of RIG, underlying immune deficiency?
- Shill NEJM
57 year old, previously healthy man

- **Category 3** exposure on hand - water mongoose
- **3.5 hours:** cell culture vaccine IMI into deltoid
- **5 hours:** RIG (20IU/kg) into wounds + wound cleaning with Eusol
- **Vaccine course:** days 3, 7, 14
- **Day 24:** onset of rabies-like illness, pos rabies PCR (saliva), rabies IgM 1:256, IgG 1:512 in serum (IFA)
- **Day 30:** died, rabies PCR and FA pos on brain, culture negative

NICD communiqué 2004
Reasons for failure of PEP?

- Correct PEP procedure
- Vaccine and RIG potency investigation
- Cold chain maintained
- No immune problems in patient
- **Possible causes of failure:** inadequate wound cleaning, penetrating wound with direct introduction of virus into nerve tissue?

NICT communique 2004
FAILED POST-EXPOSURE PROPHYLAXIS?
Special Pathogens Unit – NICD, Sandringham-Johannesburg – the referral center for human rabies in southern Africa

• On average the SPU confirms 7-10 cases annually and the majority of these cases are generally believed to be from contact with rabid dogs in the KwaZulu Natal Province

• In many instances patients in SA receive no PEP, partial or inadequate PEP and in some instances no history is available to determine if appropriate vaccination was provided
Rabies – uniformly fatal viral infection generally transmitted by the bite of infected animals

- Despite the availability of effective vaccines annual human deaths ~ 60,000 worldwide; ~ 98% of these preventable fatalities in Africa, Asia and Latin America - animal control, vaccination programs and effective human post-exposure prophylaxis are either not widely available, or not effectively applied

- Rabies virus strains circulating in specific species undergo genetic adaptation and evolve into distinct biotypes that differ in antigenicity and pathogenicity

- Two biotypes of rabies virus in southern Africa
  - canid viruses (*Canis familiaris, C. mesomelas, C. adustus, Otocyon megalotis*)
  - “viverrid viruses” (historical term) currently postulated to be named “mongoose” biotype or mongoose rabies virus (*Cynictis penicillata, Galerella sanguinea*)
**Mongoose biotype**

- There is a considerable antigenic and genetic diversity within isolates of mongoose biotype in comparison to the isolates of canid biotype which is closely related to the European wild (WR56) or vaccine rabies strains (PV/ERA).
- Based on pseudogene nucleotide sequence 3 canid isolates (5/91 - jackal; 421/92 – dog; 127/91 bat-eared fox) were showed to belong to mongoose rabies isolates group suggesting that biotypes may jump species boundaries.
- In South Africa, historical records show that mongoose rabies may have been described since the early 1800s, long before the introduction of canine rabies.
- First cases of confirmed rabies related to the bite by a yellow mongoose were reported in 1928 in two children in Wolmaransstad district in the NWP.
Is mongoose rabies in humans an important health issue?

There have been two recorded instances in which patients were bitten by rabid mongoose and despite receiving PEP they contracted the disease and died - apparent vaccine failure?

The mongoose biotype belongs the same rabies (“dog”) virus genotype

The vaccines strains are usually of the dog “cosmopolitan” type

The vaccines are said to protect reasonable well against all of the Group 1 lyssaviruses, that is, all the serogroup 1 rabies, EBL1, EBL2, Duvenhage and ABLV) … and would be expected to offer very good protection against the serogroup 1 viruses

Is then the “apparent” vaccine failure due to antigenic heterogeneity?

Would be sequence analysis, particularly of the neutralizing epitope sites of the glycoprotein useful to address it?

What about other factors, for example, a very rapid incubation period (less than 10 days) often caused by severe bites to the head or hands … or marginal vaccine potency (are the batches available for potency testing?)

….. these incidences have prompted us to investigate the efficacy of rabies vaccine against mongoose biotype
Methods

- Characterization of rabies isolates to confirm the biotype will be performed using partial nucleotide sequencing.

- The potency of rabies HDCV against viverrid isolates will be determined using the potency test in mouse model.
Phylogenetic tree illustrating genetic distance within the South African isolates of rabies isolates recovered from patients with history of dog (A) and mongoose (B) bite

A - rabies isolates from patients with history of dog bite

B - rabies isolates from patients with history of mongoose bite

Nucleotide divergence 19.23%

+PCR from saliva and brain but live virus could not be recovered

Case 195/2004 (Standerton, Mpumalanga) related to bite by Atilax paludinosus; is it the same strain as 878/92 (Harrismith); 668/92 (Albert); 610/96 (Somerset East); 113/91 (Beaufort West)