Rabies

• Pathophysiology
• Disease and “treatment”
• Epidemiology
• Who needs post-exposure prophylaxis (PEP)?
• How to give PEP

A Brief History of Rabies

• 23rd century BC - Eshmun's code
• 380 BC - Aristotle
• 1st century AD - Celsus “hydrophobia”
  – recognizes saliva contact required
• 1198 - Maimonides, Treatise on Poisonings
• 1584 - Fracastor “The Incurable Wound”

The Virus

• Family: Rhabdovirus (rod-shaped)
• Genus: Lyssavirus (lyssa = frenzy)
Life Cycle

Negri Bodies

Negri Bodies
**How Rabies Causes Sx**

- Production of cytokines and proinflammatory molecules, including interleukins, tumor necrosis factor, interferons, nitrous oxide and chemokines.
- Modify electrical activity, HPT axis, serotonin metabolism causing clinical features.
- Immune reaction recruits T and B cells, more cytokine and NO release, which increases the disturbance.
- Prevents cell apoptosis by virus downgrading expression of virus glycoprotein - which allows the virus to continue to spread.
- Ultimately, metabolic pools of cells are depleted by viral replication and cell death occurs.

**Presentation**

- Prodrome (lasts a few days)
  - Nonspecific with low-grade fever
  - Paresthesias or pain at bite site. Itching, burning, numbness, going up arm to face.
- Encephalitic
  - Irritability
  - Hyperactivity aggravated by thirst, fear, light, noise
  - Fluctuating consciousness
  - Phobic or inspiratory spasms (hydrophobia)
  - Autonomic dysfunction - hypersalivation, priapism
  - Progresses to coma

**Diagnosis**

- DFA of brain tissue of dead animal
  - Uses antibody against virus nucleoprotein
  - (Previously - negri bodies on histologic specimen)
- Ante-mortem human tests
  - No single test sufficient
  - Can become positive at various points in illness
  - Samples: saliva, csf, serum, skin bx
  - Saliva: isolation or RT-PCR
  - Serum, CSF - Test for ab's
  - Bx: rabies antigen in nerves at base of hair follicles

**Rabies - The Disease**

- Attack rate (bites) 5% - 60%
- Typically 30-90 day incubation period,
  - But now documented up to 7 years
- (Almost) uniformly fatal
- Classic Rabies
  - Furious (Encephalitic)
  - Dumb (Paralytic)
- Non-classic - bat rabies, Thai dogs

**Presentation**

- Paralytic
  - Limb weakness with fever
  - Progresses to coma and death
- Non-classic
  - Sensory and motor deficits
  - Brainstem signs
  - Choreiform movements
  - Ataxia, vertigo, seizures
  - Phobic spasms much rare
Treatment Protocol

- Induced Coma
- Ketamine/Amantadine (NMDA receptor agonist - anti-rabies activity in animals)
- Midazolam, barbiturates - reduce excitotoxicity and brain metabolism
- Ribavirin
- No Rabies vaccine

Survival with neurologic impairment

Treatment

- Two victims, 10 and 11, treated in 2007 with same protocol, did not survive.

Rabies

- Rare
- Incurable
- US - 2 human deaths/yr; 20-40,000 vaccinations
  - NNT = 20,000
- India - 30,000 deaths/yr, 3 million get PEP
  - NNT = 100

Rabies - Worldwide

Huge public health problem
Third world countries
India: 40,000 deaths
Primary carrier - dog

Rabies - US

Wild animals account for 92% of all rabies
Rabies In Domestic Animals
US 2005

- 76 dogs, 269 cats
- More likely feral, < 1 yr old
- Cats more susceptible
- Found in areas with endemic rabies


- Bat (38)
- Dog/Coyote (2)
- Skunk (1)
- Mongoose (1)
- Foreign (7)

Sources of Human Rabies US 1990-2007

- 2 dog/coyote (1994)
  - No domestic animal source for > 20 yrs
- 1 raccoon
- 90% of cases from bats
  - 50% no known exposure
  - Several aware of (but ignored) bite
  - 4 cases transplants (from rabid donor)
Unexplained Rabies in Three Immigrants in the US

- Oregon: 18 yo Mexican male dies of rabies; left Mexico 9 months before.
- Texas: 12 yo Laotian girl in US x 4 years, dog bite in Laos 7 years prior.

Smith et al, NEJM, 1991, 324(4), 205

Post-Exposure Prophylaxis

- $1600/series
- $30 - $60 million/year
- At least 25% unnecessary
- Deaths continue

Post Exposure Prophylaxis depends on

- Species
- Epidemiology in the area
- Whether the animal can be tested
- Consider the behavior of the animal only if domestic animal.

Rabies Transmission

- Most commonly from a bite, rarely scratches, transplant of tissues.
- Has not been transmitted by skin contact with blood, urine or feces.
- Virus must be secreted in saliva of biting animal
- Animal dies within 3 days of secretion

Rabies Animal Management

Animal Captured

- Domestic animal (Dog, cat, ferret)
  - Observe for 10 days. If becomes ill, begin prophylaxis
  - Abnormal behavior or appears ill, sacrifice immediately and test
- Skunk, Raccoon, Fox, Bat and most other carnivores
  - Assume rabid and begin prophylaxis
  - Sacrifice and test immediately
  - Continue Rx as indicated
Rabies Animal Management

Animal Not Captured

- **Low risk species**
  - Most livestock, domestic animals, small rodents
  - Consult local public health officials, rarely need Rx
- **High risk species:** Begin prophylaxis
- Discuss with local public health officials
  - San Francisco: (415) 554-2830
  - Contra Costa: (925) 313-6740; (925) 646-2441
  - San Mateo: (650) 363-4981

Risk of Rabies Transmission in US

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Low Risk</th>
<th>Uncertain</th>
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<tbody>
<tr>
<td>Skunk</td>
<td>Dog</td>
<td>Woodchucks in mid-Atlantic states</td>
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<tr>
<td>Raccoon</td>
<td>Cat</td>
<td>Domestic animals that roam in endemic areas, particularly if unprovoked attack</td>
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<tr>
<td>Fox</td>
<td>Lagomorph</td>
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<tr>
<td>Bat</td>
<td>Rodent</td>
<td></td>
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<tr>
<td>Dog at Texas-Mexican border</td>
<td>Livestock</td>
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<tr>
<td>Wild carnivores in endemic areas</td>
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“In situations in which a bat is physically present and the person(s) cannot exclude the possibility of a bite, post-exposure treatment should be considered unless prompt testing of the bat has ruled out rabies infection.”

(MMWR, 1995)

Phone Numbers for Help

**CDC Rabies Hotline**

404-630-1050
404-639-2888

Post-Exposure Prophylaxis History

- Powdered unicorn horns, madstones
- Put hair from tail of rabid dog into the wound
- 1198: Maimonides, *Treatise on Poisons*
- 1804: Soap and water prevent rabies

Pasteur Vaccine, 1885

- Neural tissue
- 13 Injections
Modern Rabies Era

• 1950: Duck embryo vaccine
  – 23 SQ injections
  – Limited antigenicity
• 1973: Human Diploid Cell Vaccine

Rabies Post-Exposure Prophylaxis (PEP)*

• Wound care
  – Wash with soap and water; rinse.
• Passive immunity - day 0
  – Human Rabies Immune Globulin (HRIG)
  – Infiltrate as much as possible in and around wound. Remainder IM
• Rabies Diploid Cell Vaccine (RDCV)
  – Day 0, 3, 7, 14, 21

Rabies Immunoprophylaxis

Rabies Pre-Exposure Prophylaxis

• ALWAYS give both HRIG and HDCV
• Give HDCV in deltoid, not gluteal region
• Give HRIG and HDCV in separate syringes, different arms
• Pregnancy, allergy are **not** contraindications

Case #1

• A responsible pet owner leashes his dog at an outdoor café table in San Francisco while he goes in to get a cup of coffee.
• A 4 yr old boy, sitting at the next table, crawls under the table to pet the dog.
• The dog bites the child. The parents get the dog owner’s information and call you.

Dog Bites Child

Should this child start rabies prophylaxis?

• Yes
• No
Rover and Out?

The dog’s rabies shots are up to date.

• What should happen with the dog?
  – Sacrifice and test the dog
  – Quarantine the dog
  – The dog may go about as previously

Raccoon Bites Woman

• A 43 yo woman was walking her dog one evening in San Francisco.

• Suddenly, a raccoon jumps out from behind a trash bin, bites her on the knee cap, then runs away.

• Does she need rabies shots?

  Yes

Case #3

• A family calls you on a Monday morning. This past weekend they were at their cabin in New Hampshire where they’ve gone every summer for 10 years.
  • On Saturday morning, they found a dead bat in their 7 year old daughter’s room.
  • So as not to scare her, they removed the bat and buried it. They found no bites on the child.

Bats in the Bedroom

What do you advise?

1. Start rabies prophylaxis
2. Reassurance, as no bite occurred
3. Dig up the bat and test it for rabies

Please don’t feed the squirrels

Does this child need rabies prophylaxis?

1. Yes
2. No
Case #5

• A suburban family recently adopted a stray kitten.
• The kitten was examined by a vet and given a rabies vaccination.
• The kitten initially acted normally but then began attacking its owners.
• One of them comes to your office with a bite requesting antibiotics.

Krazy Kat

What would you advise (in addition to the antibiotics)?
1. Give the cat to a family that can handle it
2. Seek help from a vet for behavioral issues
3. Test the cat for rabies
4. Get a CAT scan