Rabies Cases of Interest

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Scrubs. Season 5 Episode 20. April 25 2006.

Objectives

- Discuss some notable cases of rabies infection in humans
- Review videos showcasing manifestations of the disease
- Discuss the controversial “Milwaukee Protocol”

No PEP in a Human Case

- 40-year-old farmer bitten by a stray dog in Nigeria on Jan 1
- Rabies PEP not available in the local clinic
  - Closest availability was about 60 miles away
  - Traditional remedy employed instead
- Multiple symptoms reported March 1
  - Severe headache
  - Paresthesia at wound site
  - Severe pain at wound site

Hospital Admission

- Given diclofenac and an antibiotic then referred out
- Upon admission:
  - Fever
  - Nausea
  - Paresthesia of R hand
  - Headache
  - Difficulty swallowing
  - Hydrophobia
- Saliva positive for rabies

Hydrophobia

Suriya883. "Hydrophobia in Rabies." YouTube video, 45sec. Nov 06 2009. <https://www.youtube.com/watch?v=OtiytblJzQc>.

Unusual Animal Behavior

- New puppy displaying poor appetite April 10
- Two neighbors bitten in addition to the owner 1 day prior
- Puppy not allowed to be euthanized by owner
  - Sedated, kept in quarantine
- All bite victims referred to hospital for PEP

Access to Care

- Puppy passed 18 hours into quarantine
  - Brain extracted, tested positive for rabies
- Hospital informed owner of test results
  - PEP declined
- 5 weeks later, owner presents with symptoms
  - Fever
  - R hand paresthesia
  - Difficulty swallowing
  - Hypersalivation
  - Dyspnea
  - Hydrophobia

Rabid Animal

Tsbrownie. “WARNING - MAY BE UPSETTING - Rabid Dog.” YouTube video, 1min10sec. Aug 08 2014. <https://www.youtube.com/watch?v=mr3TfXdVSnA>.

Unusual Turn of Events

- 84-year-old man awoken by bat biting hand on July 27
- Bat tests positive for rabies on July 30
  - PEP initiated in an unvaccinated individual
- HRIG 20 IU/kg administered
  - As much as possible at bite site, remainder in R thigh
- Rabies vaccine administered
  - Remaining doses on days 3, 7, and 14

Course of Events

- Pt's wife received the same treatment at the same time
- New symptoms develop on January 7
  - Severely painful R-sided facial paroxysms
  - Excessive R eye lacrimation
- Presents to ED on January 9
  - ESR elevated
  - Thought to have trigeminal neuralgia or temporal arteritis

Symptoms Persist

- Seen over the next two days for temporal artery biopsy evaluation

- Presents to ED on January 13
  - Facial paresthesia
  - Dysphagia
  - Bilateral arm/shoulder myalgias
  - R arm paresthesia
  - N&V

- Discharged w/ ondansetron same day
  - Concern for nausea from oxycodone

Return to ED

- Symptoms were worsening
  - Now with decreased oral intake secondary to dysphagia
  - R-sided paralysis
- CT negative
- Temporal artery biopsy non-concerning
- Rabies suspected
  - However, unlikely as pt received appropriate treatment

Case Conclusion

- On Jan 15, CSF shows lymphocytic pleocytosis
- Intubated due to hypoxia
- A fever developed Jan 16 that never resolved
- Care withdrawn on January 22
- CDC confirmed rabies virus on Jan 26

What Happened?

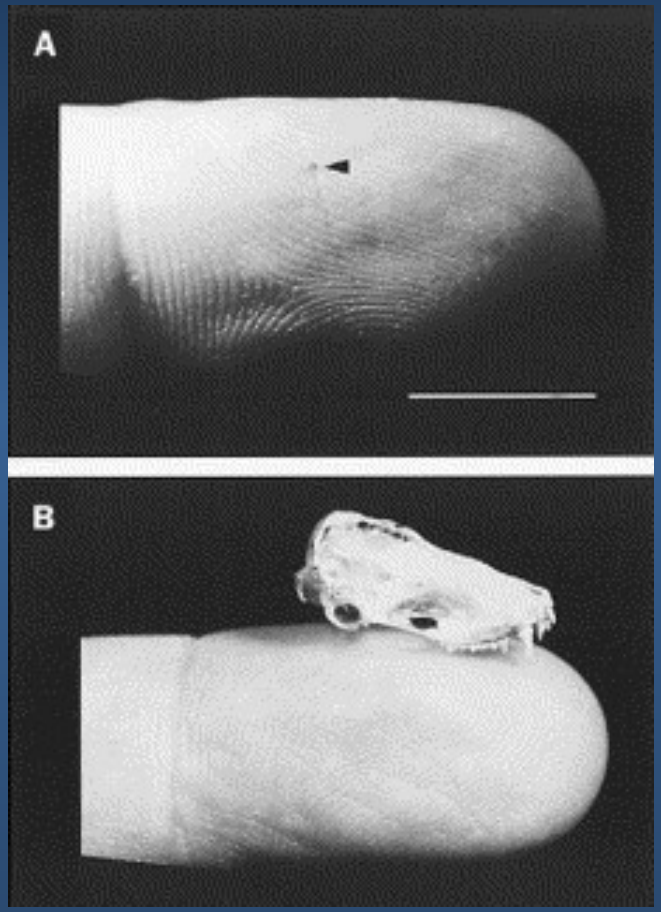
- "Host-mediated primary vaccine failure…that results from an undiagnosed immunosuppressing comorbidity is the most parsimonious explanation for the patient's fatal outcome."
- Rabies antibodies in serum and CSF were non-neutralizing
- During final hospitalization, pt positive for IgM monoclonal gammopathy of undetermined significance
- Unknown prostate adenocarcinoma discovered during autopsy
  - Metastatic to bone marrow

What Could Have Been Done?

- If the immunocompromising condition had been known:
  - Fifth vaccine dose administered at day 28
  - Titers checked with additional doses potentially administered

- HRIG not delayed and instead administered immediately
  - Unclear if this would have changed anything

Silver-Haired Bat Bite



Jackson AC, Fenton MB. Human rabies and bat bites. *Lancet*. 2001;357(9269):1714. Figure.

New Treatment Discovered…

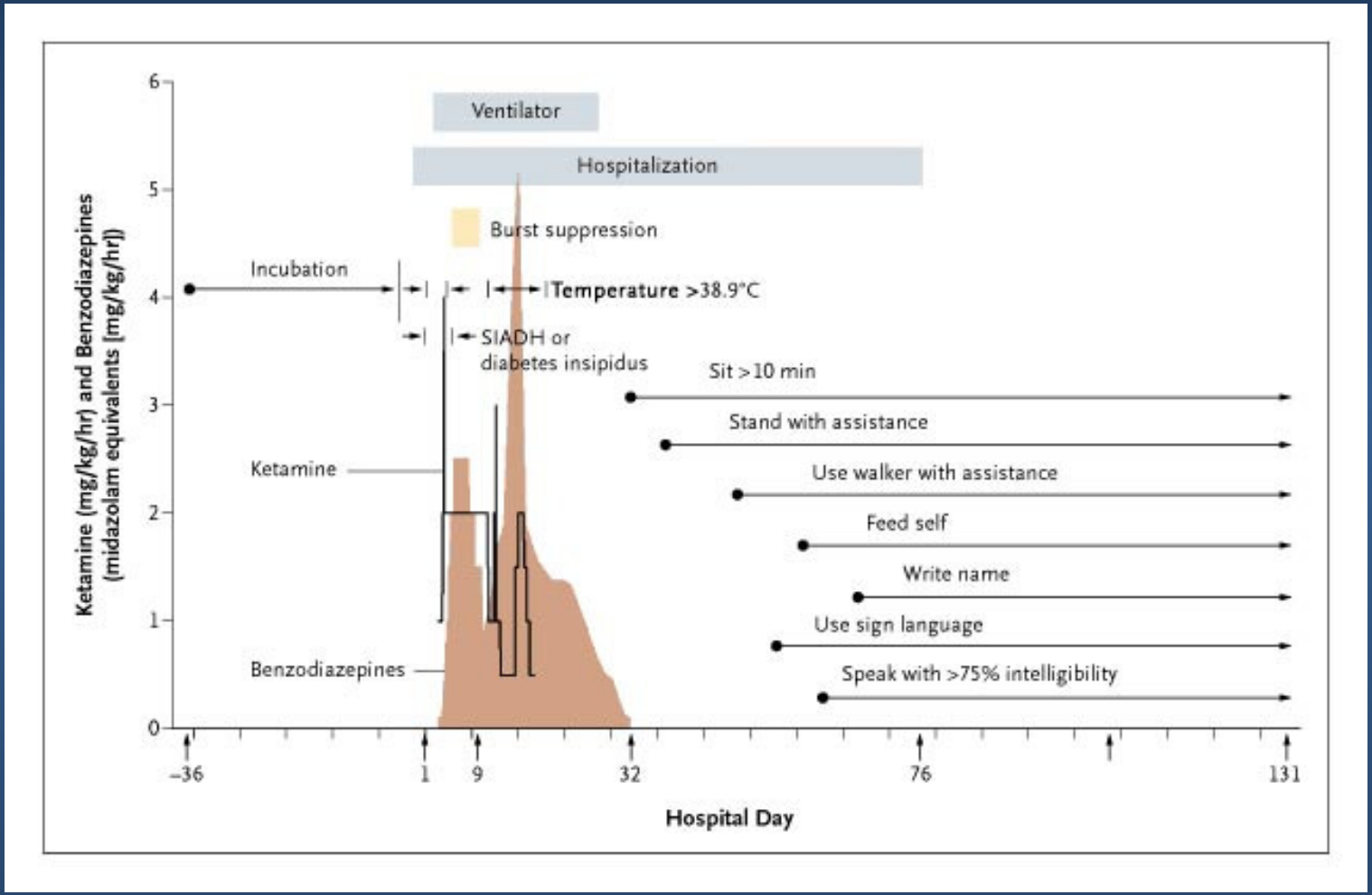
- 15-year-old girl bitten by bat at church in Milwaukee
- No PEP administered
- Fatigue and paresthesia of L hand one month after exposure
- Developments over the next few days:
  - Diplopia
  - N&V
  - Blurred vision, L leg weakness
  - Fever, slurred speech, nystagmus, L arm tremor
- Intubated after experiencing dysregulated swallowing

Aggressive Approach

- Pt's parents offered hospice vs a radical approach

- The radical approach was elected:
  - Ketamine 2 mg/kg/hr + Midazolam 1-3.5 mg/kg/hr
    - Targeting 1-2 seconds of cerebral activity interspersed
  - Red cell transfusion to maintain Hgb > 10
  - Mechanical ventilation targeting arterial normoxia, mild hypercapnia
  - Heparin 10 U/kg/hr
  - Ribavirin 16 mg/kg q6h initiated after inducing coma
  - Amantadine 200 mg daily
  - Supplemental doses of phenobarbital given as needed
    - Ultimately, midazolam switched to diazepam

Hospital Course



Willoughby Jr RE, Tieves KS, Hoffman GM, et al. Survival after treatment of rabies with induction of coma. *N Engl J Med*. 2005;352(24):2508-14. Figure 2.

Sequelae

- Choreoathetosis
  - Resolved in the next 1-2 years
- Ongoing gait difficulties and fluctuating dysarthria
- No apparent change in cognitive function from prior
- Able to perform daily activities without issue

Milwaukee Protocol

- Modifications made to it over the years
  - Most recently, no ribavirin or barbiturates
  - Agents against cerebral vasospasm added including nimodipine
- Significant controversy about actual success
  - Much of the purported data is not readily available
- Most recent studies suggest lack of efficacy
  - Potential for harm beyond the infection alone

Table 3: Summary of the Main Components of the Milwaukee Protocol, version 4.0[6]

Recommendations	Rationale	Comments
General recommendations		
No rabies vaccine or rabies immunoglobulin	Potentially decreased survival due to impaired antibody production	controversial, but beyond the scope of this review
Maintain isolation	Prevent exposures to health care workers and visitors	
Transfer to tertiary care center	For critical care management and monitoring	
Gain central access and start enteral feeds	Usual ICU protocol for expected long term ICU stay	
Maintain euglycemia, euthermia, euvolemia, eunatremia, and eucarbia	Maintain homeostasis	
DVT prophylaxis	Patients immobile for long periods	
Therapeutic coma		
Therapeutic coma for first week	To reduce mortality related to autonomic instability	merits serious reconsideration
Use ketamine as a sedative	Achieve sedation and NMDA receptor antagonism	merits serious reconsideration
Consider benzodiazepines	"minimizes vascular reactivity" during suctioning and turning	
Avoid propofol	Causes "over sedation"	
Avoid barbiturates*	Immunosuppressant	
NMDA receptor antagonism		
Amantadine (also ketamine (see above))	Antiviral agent; NMDA receptor antagonism	merits serious reconsideration
Cerebal vasospasm recommendations		
Nimodipine prophylaxis	Reduces vasospasm rates	merits serious reconsideration
Supplement vitamin C and sapropterin	Reduces vasospasm rates	merits serious reconsideration
TCD monitoring during first two weeks	Monitor for signs of vasospasm	merits serious reconsideration

ICU = intensive care unit, DVT = deep vein thrombosis, NMDA = n-methyl d-aspartate, TCD = transcranial dopplers.
*Phenobarbital was used for maintain a burst-suppression pattern on the electroencephalogram for therapeutic coma for the index case[4].

Zeiler FA, Jackson AC. Critical appraisal of the Milwaukee Protocol for rabies: this failed approach should be abandoned. *Can J Neurol Sci*. 2016;43(1):44-51. Table 3.

Table 2: Therapy in all 29 cases of human rabies occurring in the United States, Canada, and United Kingdom during the period 2005-2014. Twelve cases (41%) received major components of the Milwaukee protocol (therapeutic coma and ketamine). Therapy failed in all; the only survivor (Case No. 14) did not have neutralizing anti-rabies virus antibodies and likely did not have rabies,[39] similar to Case No. 8, who did not receive any specific therapy and did not require critical care.[41]

Case No.	Outcome/ Year of Death	Age	State/ Provinceor Country in United Kingdom	Therapeutic Coma	Ketamine	Amantadine	Ribavirin	Reference (s)
United States								
1	2005	10	MS	No	No	No	No	42
2	2006	16	TX	No	No	No	No	43
3	2006	10	IN	Yes	Yes	Yes	Yes	11
4	2006	11	CA	Yes	Yes	Yes	Yes	11
5	2007	46	MN	No	No	No	No	44
6	2008	16	CA	No	No	No	No	45
7	2008	55	MO	Yes	Yes	Yes	No	17
8	Survived,* 2009	17	TX	No	No	No	No	41
9	2009	43	IN	No	No	No	No	46
10	2009	55	MI	No	No	No	No	47
11	2009	42	VA	Yes	Yes	No	No	48
12	2010	19	LA	No	No	No	No	49
13	2011	70	WI	No	No	No	No	50
14	Survived,* 2011	8	CA	Yes	Yes	Yes	No	39
15	2011	73	NJ	No	No	No	No	51
16	2011	25	NY	Yes	Yes	No	No	26
17	2011	20	NC	No	No	No	No	52
18	2011	40	MA	No	No	No	No	53
19	2011	46	SC	No	No	No	No	54
20	2012	63	MA	Yes	Yes	No	No	28
21	2012	34	CA	No	No	No	No	55
22	2012	49	MD	No	No	No	No	52
23	2013	28	TX	Yes	Yes	Yes	No	34
24	2014	52	MO	No	No	No	No	**
Canada								
25	2007	73	AB	Yes	Yes	Yes	Yes	13,56
26	2012	41	ON	Yes	Unknown	Unknown	Unknown	30
United Kingdom								
27	2005	37	England	No	No	No	No	57,58
28	2009	37	Northern Ireland	Yes	Yes	Yes	Yes	22
29	2012	58	England	Yes	Yes	Yes	No	33

*Two patients recovered from an illness without the presence of neutralizing anti-rabies virus antibodies, raising very serious doubts about a diagnosis of rabies.

**Personal communication, Jesse Blanton, Center for Disease Control and Prevention, Atlanta, GA, USA.

Zeiler FA, Jackson AC. Critical appraisal of the Milwaukee Protocol for rabies: this failed approach should be abandoned. *Can J Neurol Sci*. 2016;43(1):44-51. Table 2.

Current Status

- The critical care aspect of the protocol is key

- No evidence that the "key" elements of protocol are efficacious
  - Therapeutic coma
  - Ketamine infusion
  - Amantadine
  - Screening/prophylaxis/management of cerebral vasospasm

Protocol Conclusion

- Best approach is administration of immune globulin/vaccine
- Further management via routine critical care procedures
- “Milwaukee Protocol” is not recommended at this time

Conclusion

- Immunocompromised individuals warrant more aggressive care
  - Additional vaccination, monitoring of immune response
- Timing critical
  - Consider type of animal, wound sites and severity, immune status, region