MAJOR ARTICLE

Clinical Features of Dog- and Bat-Acquired Rabies in Humans

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Background. Clinical differences in rabies due to canine and bat rabies virus variants have been noted, but no detailed studies have been reported to support these observations.

Methods. Using the *Morbidity and Mortality Weekly Report* and PubMed, we identified 142 case reports of rabies from North America, South America, Europe, Africa, and Asia. We systematically abstracted 126 selected data elements and compared clinical features and investigation results in dog- and bat-acquired cases of rabies.

Results. Survivors and cases acquired from aerosolized viral exposure or tissue/organ transplant were excluded (n = 20). Of 122 cases, 49 (40.2%) were dog-acquired and 54 (44.3%) were bat-acquired. Bat-acquired cases of rabies were more often misdiagnosed and lacked a bite history. Encephalopathy, hydrophobia, and aerophobia were more common in dog-acquired rabies. Abnormal cranial nerve, motor, and sensory examinations, tremor, myoclonus, local sensory symptoms, symptoms at the exposure site, and local symptoms in the absence of a bite or scratch were more common in patients with bat-acquired rabies, as was increased cerebrospinal fluid protein ($P = .031$). Patients with paralytic rabies had longer survival times than those with encephalitic rabies, and also had shorter incubation periods if they had received postexposure prophylaxis.

Conclusions. Clinical differences in dog- and bat-acquired rabies may reflect differences in the route of viral spread of rabies virus variants in the nervous system, although certain variants could cause more severe dysfunction in neuronal subpopulations. Recognition that bat-acquired rabies may present with different clinical manifestations than dog-acquired rabies may help improve the early diagnosis of rabies.

Keywords. rabies; dog; bat; human; neurological.

Human rabies continues to be an important public health problem worldwide [1]. Most human cases of rabies occur in resource-poor or resource-limited countries where transmission to humans occurs by dog bites. However, most indigenous cases of human rabies in North America are transmitted from bats, and the incidence of human rabies acquired from bats has increased 3-fold between the periods 1950–1989 and 1990–2007 [2]. Rabies is endemic in several other wildlife vectors such as skunks, foxes, and raccoons, but transmission to humans by these vectors is relatively uncommon [3].

Although clinical differences in rabies due to canine and bat rabies virus variants have been noted previously [4], no detailed studies support these observations. Awareness of clinical differences between dog- and bat-acquired rabies may have implications for suspecting a diagnosis of rabies and may provide insights into potential differences in the pathogenesis of rabies caused by different rabies virus variants. We performed a detailed analysis of published cases to determine whether clinical and laboratory differences exist in dog- and bat-acquired rabies in humans.

METHODS

Using the *Morbidity and Mortality Weekly Report* and PubMed, we identified 142 case reports in English of

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rabies published in North America, South America, Europe, Asia, and Africa between 1958 and 2011. We systematically abstracted 126 data elements (Supplementary Table 1), including demographic data (14), clinical features (67), and results of investigations (45). Because it is not common practice in case reports of rabies to report negative data for clinical features, many variables had missing results. In a sensitivity analysis, we imputed the clinical features that were not reported as negative and repeated the analysis.

Cases were classified as dog- or bat-acquired based on viral variant typing by reverse transcription polymerase chain reaction/nucleotide sequencing, or monoclonal antibody characterization, or on the basis of reported animal exposure if no viral typing was available. Cases were further classified as encephalitic, paralytic, or indeterminate (lack of distinguishing features or insufficient clinical information) after review of case histories by one of the authors (A.C.J.).

Clinical symptoms or signs were defined as early onset if they developed within the first 7 days of disease onset and late onset if symptoms or signs developed after this time. Naturally acquired rabies cases were defined as acquired from a known animal vector or a presumed but unknown animal vector, and not acquired from an organ or tissue transplant. Survival times were defined as the number of days between the onset of symptoms of rabies and death.

Categorical variables are reported as frequency (percentage), and continuous variables are reported as median (interquartile range [IQR]). We compared bat- and dog-acquired cases with respect to site of exposure, incubation and survival times, and investigations using χ^2 or Fisher exact tests for categorical variables, and Mann-Whitney *U* tests for continuous variables. The Kruskal-Wallis test was used when comparing >2 independent samples. We did not perform statistical comparisons for clinical characteristics due to missing data and the large number of characteristics reported. Statistical analyses were conducted using PASW Statistics version 18 (SPSS Inc, Chicago, Illinois).

RESULTS

Of 142 cases, 122 (86.5%) were naturally acquired and they are listed by vector and geographical region in Supplementary Table 2. Of the naturally acquired cases, 49 (40.2%) were dog-acquired and 54 (44.3%) were bat-acquired, and were analyzed in more detail. Nine (7.4%) cases were transmitted from an unknown exposure and 10 (8.2%) cases were acquired from other animals, including skunk (n = 4), cat (n = 2), fox (n = 2), bobcat (n = 1), and raccoon (n = 1). Patients with rabies who survived (n = 4) [5–8], patients with transplant-associated cases (n = 15) [9–15], and 1 patient with rabies acquired from aerosolized viral exposure [16] were excluded because of assumed fundamental differences in the pathogenesis of these cases.

Table 1. Clinical Types of Rabies

Type of Rabies	Encephalitic, No. (%)	Paralytic, No. (%)	Indeterminate, No. (%)	*P* Value
Naturally acquired	89 (73.0)	18 (14.6)	15 (12.3)	
Dog-acquired	34 (69.4)	8 (16.3)	7 (14.3)	
Bat-acquired	44 (79.6)	6 (11.1)	5 (9.26)	
				.37

The median age of patients with naturally acquired rabies was 36.5 years (IQR, 17.3–53 years); 25.4% were <18 years of age. Most patients were male (77.1%), and this was similar between dog- and bat-acquired cases ($P = .232$). The proportion of encephalitic or paralytic rabies did not differ between dog- and bat-acquired cases ($P = .37$, Table 1).

Rabies Exposures

Case exposures and reports came from locations in North America (United States, Canada, Mexico, and Greenland), Central America, South America, Europe, Africa, and Asia. Many exposures and reports of naturally acquired rabies occurred in the United States (39.3% and 73.8%, respectively). Dog-acquired rabies exposures occurred in Asia (36.7%), Africa (22.4%), and Mexico (14.3%), whereas 68.5% of bat-acquired rabies cases presented in the United States or Canada. Of 21 cases (17.2%) imported into the United States or Canada from other countries, 19 were dog-acquired. All 17 reports from Europe were imported cases. The location of exposure of 19.7% of cases was unknown.

Patients with dog-acquired cases of rabies were more likely to have been bitten ($P < .001$), especially on the leg ($P = .036$) or at multiple sites ($P = .036$), than were patients with bat-acquired cases. Patients with bat-acquired rabies were 3 times more likely to have had no known exposure ($P = .024$) and consequently an unknown anatomical site of exposure ($P = .001$; Table 2).

Incubation Periods

Median incubation time for all naturally acquired cases was 54 days (IQR, 30.5– 91 days). Accurate incubation times were only available for 31 (57.4%) bat-acquired and 42 (86%) dog-acquired cases of rabies. The median incubation times for dog-acquired (64.5 days [IQR, 42.3–101 days]) and bat-acquired cases (51 days [IQR, 26.5–91.5 days]) were similar ($P = .063$). The median incubation time for encephalitic rabies was 55 days (IQR, 30.5–90.5 days) and was similar to that for paralytic rabies of 48 days (IQR, 28–122 days) ($P = .969$). There was no difference in incubation times between cases in which patients were exposed on the face, upper extremity, or lower extremity ($P = .753$).

Table 2. Exposure Types and Exposure Sites in Dog- and Bat-Acquired Cases of Rabies

Exposure	Dog-Acquired, No. (%)	Bat-Acquired, No. (%)	*P* Value
Exposure type			
Bite only	37 (75.5)	16 (29.6)	<.001
Scratch only	0	1 (1.9)	1
Bite and scratch	0	2 (2.7)	1
Direct contact, no bite or scratch	7 (14.3)	16 (29.6)	.062
Shared physical space	0	4 (7.4)	.052
No known exposure	5 (10.2)	15 (27.8)	.0024
Exposure site			
Face	2 (4.1)	5 (9.3)	.297
Arm	16 (32.7)	9 (16.7)	.059
Leg	6 (12.2)	1 (1.9)	.036
Trunk	1 (2.0)	0	.271
Missing	18 (36.7)	38 (70.4)	.001
Multiple	6 (12.2)	1 (1.9)	.036

Survival Times

The median survival time for patients with naturally acquired rabies was 14 days (IQR, 9–21 days) from symptom onset. The median survival times for patients with dog-acquired (17.5 days [IQR, 11.3–22.8 days]) and bat-acquired rabies (14 days [IQR, 9.3–17 days]) were similar ($P = .102$). The median survival time was 41% shorter for encephalitic (12 days [IQR, 9–17.8 days]) than paralytic rabies (22 days [IQR, 18–28 days]) ($P < .001$).

Clinical Manifestations

Clinical manifestations and investigations recorded for cases of naturally acquired and dog- and bat-acquired rabies are shown in Table 3. Clinical features that were more common in dog- than bat-acquired rabies included encephalopathy (64.3% vs 46.2%), hydrophobia (81.5% vs 72.2%), and aerophobia (80% vs 50%). Clinical features that were more common in bat- than dog-acquired rabies included myoclonus (91.7% vs 0%), cranial nerve abnormalities (66.8% vs 57.1%), and abnormal motor (78.3% vs 64.7%) and sensory (77.3% vs 59.1%) examinations. Tremor was reported in 13 patients with bat-acquired rabies, but in only 1 patient with dog-acquired rabies.

All local symptoms were more common in patients with bat-acquired than with dog-acquired cases of rabies. Local sensory symptoms (97.5% vs 79.3%), symptoms at the bite or scratch site (87.5% vs 70.4%), and local symptoms in the absence of a bite or scratch (100% vs 85.7%) were more common in bat- than dog-acquired cases. Findings from the sensitivity analysis produced similar conclusions (Supplementary Table 3).

Diagnosis

Misdiagnosis occurred in 60.7% of all naturally acquired cases. Bat-acquired rabies (74.1%) was 65% more likely to be misdiagnosed than dog-acquired rabies (46.9%; $P = .008$). The most common diagnoses were encephalitis not yet determined (11.6%), pharyngitis (9.1%), and Guillain-Barré syndrome (5.8%). When misdiagnosed, history of a bite exposure was lacking in 70% and 35% of bat- and dog-acquired cases, respectively. Misdiagnosis occurred when patients were evaluated in countries without endemic dog rabies in 100% and 91% of misdiagnosed bat- and dog-acquired cases, respectively.

Investigations

Among all patients with naturally acquired rabies, 37.7% had computed tomographic scans of the head, 16.4% had magnetic resonance imaging scans of the brain or spinal cord, 29.5% had electroencephalography, and 5.7% had electrodiagnostic studies (Supplementary Table 3).

Cerebrospinal fluid (CSF) analysis was performed on 81 (66.4%) patients with naturally acquired cases of rabies. The median CSF total nucleated cell count (TNCC) and protein was 14 cells/mm^3 (IQR, 5–70 cells/mm^3) and 70 mg/dL (IQR, 45–104 mg/dL), respectively, for patients with naturally acquired cases of rabies. There was no difference between dog- and bat-acquired cases in CSF TNCC (11 cells/mm^3 [IQR, 6–42 cells/mm^3] and 11 cells/mm^3 [IQR, 1.75–79.5 cells/mm^3], respectively; $P = .853$) or protein levels [43.5 mg/dL [IQR, 26–79.8 mg/dL] and 79 mg/dL [IQR, 52–109 mg/dL], respectively; $P = .069$). Of those reported, 12 of 19 (63.16%) dog- and 19 of 43 (55.9%) bat-acquired cases had increased CSF TNCC ($P = .606$). A lymphocytic predominance was reported in most of the naturally acquired, dog-acquired, and bat-acquired cases. Two times more patients with bat-acquired (18 of 30 [60%]) than dog-acquired rabies (5 of 18 [27.8%]) had increased CSF protein ($P = .031$).

The results of antemortem investigations performed also did not differ between dog- and bat-acquired rabies. The sensitivity of antemortem investigations did not differ in dog- compared to bat-acquired rabies (Supplementary Table 4). The timing of positive test results did not differ in dog- and bat-acquired cases (Supplementary Table 5).

When tested, serum neutralizing antirabies virus antibodies were more commonly detected in patients with paralytic (9 of 10 [90%]) than in those with encephalitic (24 of 45 [53.3%]) rabies ($P = .032$). The median number days from onset of symptoms to a positive serum antibody result did not differ between encephalitic (8 days) and paralytic cases (7 days, $P = .876$).

Brain biopsy was performed on 6 (4.9%) and postmortem brain tissue analysis on 87 (71.3%) of patients with naturally acquired rabies. The results of rabies virus antigen, viral isolation, histological inflammation, or Negri bodies did not differ between dog- and bat-acquired rabies.

Table 3. Clinical Features of Rabies in Naturally Acquired and Dog- and Bat-Acquired Cases of Rabies

Clinical Feature	Naturally Acquired[a] (n = 122)			Dog-Acquired (n = 49)			Bat-Acquired (n = 54)			
	No.	no.	% Yes (no./No.)	No.	no.	% Yes (no./No.)	No.	no.	% Yes (no./No.)	Dog-Bat Difference
Rabies specific										
Headache	31	31	100.0	12	12	100.0	12	12	100.0	0.0
Malaise	80	80	100.0	29	29	100.0	36	36	100.0	0.0
Meningismus	10	8	80.0	3	2	66.7	3	2	66.7	0.0
Insomnia	10	10	100.0	4	4	100.0	4	4	100.0	0.0
Hallucinations	23	23	100.0	8	8	100.0	13	13	100.0	0.0
Sore throat	33	33	100.0	9	9	100.0	17	17	100.0	0.0
Slurred speech	14	14	100.0	2	2	100.0	8	8	100.0	0.0
Late-onset encephalopathy	19	19	100.0	6	6	100.0	10	10	100.0	0.0
Biting	4	4	100.0	1	1	100.0	2	2	100.0	0.0
Fever	84	82	97.6	32	31	96.9	39	38	97.4	−0.6
Hyperarousal	74	73	98.6	28	28	100.0	37	36	97.3	2.7
Hydrophobia	53	41	77.4	27	22	81.5	18	13	72.2	9.3
Larynx/face spasms	13	12	92.3	6	5	83.3	5	5	100.0	−16.7
Encephalopathy	106	54	50.9	42	27	64.3	52	24	46.2	18.1
Aerophobia	22	16	72.7	15	12	80.0	6	3	50.0	30.0
Myoedema	1	1	100.0	1	1	100.0	0	0	0.0	100.0
Priapism	3	3	100.0	0	0	0.0	3	3	100.0	−100.0
Bite site										
Local symptoms without bite	33	32	97.0	7	6	85.7	24	24	100.0	−14.3
Symptoms at bite site	64	36	56.3	27	19	70.4	16	14	87.5	−17.1
Any local sensory symptoms	79	70	88.6	29	23	79.3	40	39	97.5	−18.2
Weakness	43	31	72.1	17	10	58.8	22	18	81.8	−23.0
Pain	58	49	84.5	21	15	71.4	30	29	96.7	−25.2
Paresthesias	38	28	73.7	15	9	60.0	18	16	88.9	−28.9
Pruritus	11	1	9.1	6	0	0.0	3	1	33.3	−33.3
Numbness	34	23	67.6	13	6	46.2	17	15	88.2	−42.1
Other										
Tremor	14	14	100.0	1	1	100.0	13	13	100.0	0.0
Convulsive seizures	25	24	96.0	11	11	100.0	7	7	100.0	0.0
Nonconvulsive seizures	3	3	100.0	2	2	100.0	1	1	100.0	0.0
Status epilepticus	5	5	100.0	1	1	100.0	3	3	100.0	0.0
Autonomic dysfunction	18	18	100.0	5	5	100.0	11	11	100.0	0.0
Sweating	14	14	100.0	3	3	100.0	6	6	100.0	0.0
Piloerection	0	0	0.0	0	0	0.0	0	0	0.0	0.0
Hypersalivation	35	33	94.3	14	12	85.7	18	18	100.0	−14.3
Ataxia	14	10	71.4	4	2	50.0	8	6	75.0	−25.0
Myoclonus	12	11	91.7	0	0	0.0	12	11	91.7	−91.7
Chorea	2	2	100.0	0	0	0.0	2	2	100.0	−100.0
Dilated pupils	2	2	100.0	0	0	0.0	2	2	100.0	−100.0
Motor-sensory examination										
Fasciculations	6	6	100.0	3	3	100.0	2	2	100.0	0.0
Hemiparesis	46	4	8.7	16	1	6.3	21	1	4.8	1.5
Late-onset weakness	49	36	73.5	21	16	76.2	18	14	77.8	−1.6
Ascending flaccid weakness	49	35	71.4	21	16	76.2	18	13	72.2	4.0
Radicular sensory pattern	44	9	20.5	18	5	27.8	20	4	20.0	7.8
Lower motor neuron weakness	42	20	47.6	16	7	43.8	19	10	52.6	−8.9

Table 3 continued.

Clinical Feature	Naturally Acquired[a] (n = 122) No.	no.	% Yes (no./No.)	Dog-Acquired (n = 49) No.	no.	% Yes (no./No.)	Bat-Acquired (n = 54) No.	no.	% Yes (no./No.)	Dog-Bat Difference
Abnormal deep tendon reflexes	38	19	50.0	17	8	47.1	17	10	58.8	−11.8
Abnormal motor examination	49	35	71.4	17	11	64.7	23	18	78.3	−13.6
Peripheral sensory pattern	46	17	37.0	21	7	33.3	19	9	47.4	−14.0
Abnormal sensory examination	50	31	62.0	22	13	59.1	22	17	77.3	−18.2
Hemisensory sensory pattern	45	6	13.3	18	1	5.6	21	5	23.8	−18.3
Cranial nerves										
Dysphagia	65	59	90.8	25	21	84.0	31	29	93.5	−9.5
Bilateral facial weakness	21	6	28.6	11	3	27.3	6	1	16.7	10.6
Cranial nerve abnormality	37	25	67.6	14	8	57.1	16	11	68.8	−11.6
Unilateral facial weakness	25	8	32.0	11	3	27.3	9	4	44.4	−17.2
Ptosis	20	5	25.0	9	1	11.1	8	3	37.5	−26.4
Ophthalmoplegia	26	11	42.3	9	1	11.1	9	4	44.4	−33.3
Anisocoria	23	11	47.8	9	2	22.2	10	7	70.0	−47.8
Late complications										
Coma	89	89	100.0	31	31	100.0	42	42	100.0	0.0
Cardiovascular complications	55	55	100.0	28	28	100.0	20	20	100.0	0.0
Respiratory complications	44	44	100.0	17	17	100.0	22	22	100.0	0.0
Gastrointestinal complications	3	3	100.0	2	2	100.0	1	1	100.0	0.0
SIADH	4	4	100.0	2	2	100.0	2	2	100.0	0.0
Diabetes insipidus	6	6	100.0	3	3	100.0	2	2	100.0	0.0

No., sum of number of reported positive and negative values for each variable; no., number of variables reported as positive. Missing information for each individual variable is excluded. Differences are expressed as an absolute percentage difference in positive values between dog- and bat-acquired cases. A positive difference indicates that a higher percentage of dog-acquired cases were positive for the indicated variable, and a negative difference indicates that a higher percentage of bat-acquired cases were positive for the indicated variable.

Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone secretion.

[a] Naturally acquired cases included cases acquired from a known animal vector or a presumed but unknown animal vector, and not acquired from organ or tissue transplant.

Postexposure Prophylaxis

Of all patients with naturally acquired cases, 19 (15.6%) received postexposure prophylaxis (PEP), including rabies vaccine (n = 15 [78.9%]) individually or in combination with immunoglobulin (n = 4 [21.1%]). There was no difference in the proportion of patients with dog- or bat-acquired rabies who received PEP (16.3% vs 7.9%; $P = .111$). Incubation and survival times were compared for patients who had received PEP versus those who had not (Table 4). Among naturally acquired cases of rabies, the median incubation times were 50% shorter in patients who received PEP (31 days [IQR, 24.5–52.5 days]) than in those who had not received PEP (61.5 days [IQR, 34.5–98.3 days]; $P = .002$). Similarly, the median survival times were 60% shorter in patients who received PEP (9 days [IQR, 8–14.5 days]) than in those who had not received PEP (15 days [IQR, 11–21 days]; $P = .024$). Differences in incubation periods or survival times were not observed among dog- or bat-acquired cases.

Paralytic cases (n = 5 [44.4%]) were more likely than encephalitic cases (n = 7 [7.9%]) to have received PEP ($P = .029$). The median incubation time for paralytic cases was 4.2 times longer for those who had not received PEP (105 days [IQR, 48.3–192 days]) versus those who had (25 days [IQR, 19–29 days], $P = .03$). In encephalitic cases, the median survival time was 1.6 times longer in those who had not received PEP (14 days [IQR, 9.3–19 days]) versus those who had (9 days [IQR, 8–10 days], $P = .035$).

DISCUSSION

In the United States and Canada, bats have become the important rabies vector for rabies virus transmission to humans [2]. Bat bites are often small and superficial and may not be recognized, particularly if unwitnessed [17]. In one series, 11% of bat-acquired rabies cases were diagnosed postmortem [2]. Clinicians in the United States, Canada, Europe, and other regions with a low incidence of human rabies may not consider rabies

Table 4. Incubation and Survival Times in Naturally, Dog- and Bat-Acquired Rabies and in Encephalitic and Paralytic Cases of Rabies With Any Postexposure Prophylaxis or With None

	Naturally Acquired		Dog-Acquired		Bat-Acquired		Encephalitic		Paralytic	
PEP Status	I (days)	S (days)	I (days)	S (days)	I (days)	S (days)	I (days)	S (days)	I (days)	S (days)
No PEP										
No.	64	98	34	38	28	51	52	78	8	13
Median	61.5	15	72.5	18.5	49	14	59.5	14	105	22
Min	14	2	26	2	14	6	14	2	18	17
Max	731	73	741	73	358	71	730	71	731	39
25th percentile	34.5	11	42	10	25	9	32.5	9.3	48.3	19
75th percentile	98.3	21	91.8	22	90.3	17	92.5	19	192	28
Any PEP										
No.	19	19	8	8	3	3	7	7	5	5
Median	31	9	36.5	9.5	55	11	32	9	25	23
Min	17	4	24	4	25	8	21	7	17	8
Max	701	133	701	27	59	23	701	14	42	133
25th percentile	24.5	8	71.8	20	53.5	13	24	8	19	10
75th percentile	52.5	14.5	581	28	172.5	18.5	50	10	29	27
Comparison of median times in cases who received vs did not receive PEP										
P Value	*.002*	*.024*	.12	.061	.826	.721	.156	*.035*	*.030*	.849

Statistically significant results ($P < .05$) are indicated in italics.

Abbreviations: I, incubation time; Min, minimum value; Max, maximum value; PEP, postexposure prophylaxis; S, survival time.

in the differential diagnosis of acute neurological illnesses, especially if a history of an animal bite is not volunteered. In our review, cases of dog- and bat-acquired rabies were more likely to be misdiagnosed in nondog rabies-endemic countries. Furthermore, in dog- and bat-acquired cases lacking a bite history, misdiagnosis was more common. This highlights the importance of a bite history in rabies diagnosis. Early consideration of rabies is important for the implementation of appropriate barrier techniques by healthcare workers to reduce the need for rabies PEP [18].

Recognition that the clinical manifestations of bat-acquired rabies may be different from the classical findings described in dog-acquired rabies may lead to a more prompt diagnosis in some cases. Specifically, we found that patients with dog-acquired rabies more commonly had encephalopathy, hydrophobia, and aerophobia than did patients with bat-acquired rabies, whereas patients with bat-acquired cases more commonly had tremor; myoclonus; cranial nerve, motor, or sensory deficits on neurological examination; or local motor or sensory symptoms (Table 3). Differences in the histopathology or rabies virus antigen distribution have not been reported in fatal human cases due to different rabies virus variants, although these have not been comprehensively evaluated in any published report. We speculate that clinical differences in dog- and bat-acquired human cases predominantly reflect differences in the viral pathways of spread of the rabies virus variants in the nervous system. Alternatively, different variants may induce more severe dysfunction in a subpopulation of neurons or cause previously unrecognized structural changes [19]. Studies of rabies in an animal model have been performed in skunks using intramuscular inoculation with a wild-type (street) virus variant [20–22]. Dog rabies virus likely spreads in a pathway similar to skunk rabies virus [21, 22]. However, no experimental studies have been performed using bat virus variants with superficial exposures, which would mimic the natural situation.

Bat rabies virus may spread from superficial tissues and either directly or indirectly to local sensory root ganglia. This may explain why patients with bat-acquired rabies more commonly had local sensory symptoms as well as focal neurological deficits on cranial nerve, motor, or sensory examinations.

Hydrophobia and aerophobia, seen more frequently in dog-acquired cases, are thought to be due to selective infection of neurons that inhibit inspiratory neurons in the region of the nucleus ambiguous in the medulla [23]. Viral spread into this region of the medulla may be critically important for the development of these characteristic clinical features. Viral spread involving the medulla in dog-acquired rabies may also explain why more patients with dog-acquired rabies had encephalopathy.

The tremor and myoclonus observed more frequently in bat-acquired rabies could reflect involvement of structures and circuits including the peripheral nerves, brainstem, thalamus, basal ganglia, cerebellum, and/or cerebral cortex [24] and in

the spinal cord, brainstem, subcortical region, and/or cerebral cortex [25], respectively. Further information about the clinical features of the tremor and myoclonus could help in determining the anatomical site(s) of involvement for these neurological signs.

Patients with bat-acquired rabies were more likely to have increased CSF protein than were patients with dog-acquired cases. This suggests that bat-acquired rabies viral variants may have a more pronounced effect on endothelial cell permeability involving the blood–CSF barrier.

Encephalitic and paralytic types of rabies are distinguished clinically by the presence of episodes of generalized arousal or hyperexcitability and early flaccid muscle weakness, respectively [18]. This study confirms longer survival in patients with paralytic rabies, likely due to later involvement of vital brainstem centers. We did not find that either encephalitic or paralytic rabies was more associated with dog- or bat-acquired rabies.

Patients with naturally acquired cases of rabies who received PEP had shorter incubation and survival times than those who did not. This supports the previously described "early death" phenomenon in cases of animal rabies unsuccessfully treated with rabies vaccine [26, 27]. Shorter incubation or survival times were not observed in the subgroups of patients with bat- or dog-acquired human rabies who received PEP, as has been previously suggested [28]. Patients with encephalitic rabies who received PEP also had shorter survival times than those who did not, which we speculate may occur as a result of immunopathological mechanisms with immune-mediated neuronal injury.

Patients with paralytic rabies were more likely to have received PEP. It has been suggested that unsuccessful postexposure vaccination may be a risk factor for paralytic rabies [29]. We found that patients with paralytic cases of rabies are more likely to have detectable serum antibodies than those with encephalitic cases, independent of the timing of the test for antibody detection. Finally, patients with paralytic rabies who received PEP had shorter incubation times than those who did not. These observations support the hypothesis that paralytic rabies involves an immune response against peripheral nerves [30, 31], and that unsuccessful vaccination may prompt a more severe antibody response resulting in paralytic rabies.

Limitations of this study are noted. The evaluators were not blinded with regard to the animal source or viral variant in abstracting data elements. More important, most case reports were neither assessed nor written by clinical neurologists and, hence, lacked detailed neurological assessments. Furthermore, the information provided in case reports was not standardized.

Recognition that bat-acquired cases of rabies can present differently from dog-acquired cases may increase the index of suspicion for clinicians evaluating suspected cases of rabies. Further research into the pathogenesis of rabies in natural animal models will be needed to improve our understanding of the complex events that result in the distinctive clinical manifestations of rabies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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