91

A 20-Year-Old Male from India With Fever and Quadriparesis

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Clinical presentation

History

A previously healthy 20-year-old man from southern India is admitted to a local hospital with fever and quadriparesis.

He has had fever for 4 days, followed by tingling and weakness initially in his left leg, subsequently involving all four limbs over the next 2 days. He gives a history of a stray dog bite (WHO category III) on his left lower limb 1 month before onset of symptoms, for which he received five doses of anti-rabies vaccine (purified chick embryo cell vaccine), but no rabies immunoglobulin (RIG).

Clinical Findings

On admission, he is conscious and his mental functions are normal (GCS 15/15). His blood pressure is 110/70 mmHg, pulse 90 beats per minute, respiratory rate 26 breaths per minute and temperature 38.5°C (101.3°F). Neurological examination reveals a flaccid, areflexic quadriparesis.

Laboratory Results

His blood investigations including serum electrolytes, renal and liver function test are normal. Cerebrospinal fluid (CSF) shows 52 mg/dL protein (reference: 15–50mg/dL), 60 mg/dL glucose (reference: 50–75mg, provided a normal serum glucose) and 340 cells/mm^3 (60% polymorphs and 40% lymphocytes; normal $\leq$5 cells/mm^3).

Questions

1. You are suspecting rabies. How could you secure the diagnosis? What are the differentials?
2. How could rabies have been prevented in this case?

Discussion

A 20-year-old male Indian with a history of dog-bite presents with fever and rapidly progressive quadriparesis a month after the incident. He has received a full course of five active anti-rabies vaccinations, but no anti-rabies immunoglobulin.

Answer to Question 1

How Could You Secure the Diagnosis? What Are the Differentials?

A young male with a history of dog bite in a rabies-endemic country, presenting with fever and rapidly progressive ascending paresis a month later should elicit a high clinical suspicion of paralytic rabies. Laboratory confirmation must be done wherever feasible to rule out clinical mimics (Table 91.1) amenable to treatment and to institute prompt infection control measures. Testing at least three saliva samples at 3- to 6-hour intervals (owing to intermittent shedding of the virus in saliva), along with a nuchal skin biopsy for viral RNA by RT-PCR, can secure the diagnosis in most cases of the encephalitic form of rabies. Though serological diagnosis has a limited role in

TABLE 91.1 Clinical Mimics of Rabies

Syndrome or Disease
Guillain Barré Syndrome
Post-vaccination encephalomyelitis
NMDAR antibody-mediated/Autoimmune encephalitis
Campylobacter-associated summer paralysis syndrome
Cerebral malaria
Herpes simplex encephalitis
Arthropod-borne encephalitides (e.g. Japanese encephalitis, West Nile Virus encephalitis, etc.)
Poliomyelitis
B-virus (Cercopithecine herpesvirus 1) encephalomyelitis
Tetanus
Snake- or Scorpion-envenomation
Organophosphate poisoning
Illicit drug use, CNS intoxicants
Psychiatric disorders

the first week of illness, detection of rabies-specific antibodies in serum (of an unvaccinated individual) or CSF can aid in diagnosis, especially in cases where survival is prolonged beyond a week. If laboratory confirmation cannot be done ante-mortem, antigen detection by direct fluorescent antibody (dFA) test or RT-PCR on brain tissue obtained post-mortem can confirm or rule out a diagnosis of rabies (Table 91.2).

Answer to Question 2

How Could Rabies Have Been Prevented in This Case?

Prompt and appropriate post-exposure prophylaxis (PEP) after an exposure from a suspect rabid animal can prevent rabies in almost 100% of cases. True PEP failures are extremely rare and may occur because of short incubation periods resulting from multiple exposures on highly innervated areas of the body like the face, neck, hands etc. or because of direct inoculation of the virus into nerves.

In severe exposures (WHO category III) PEP consists of thorough wound washing, active vaccination with anti-rabies vaccines and passive vaccination with anti-rabies immunoglobulin (RIG). While it may take about 5 to 7 days for vaccine-induced antibodies to be produced, RIG, which is locally infiltrated into and around the wounds neutralizes the virus deposited at the site of the bite and prevents its entry into the nerves. Even though the patient received adequate doses of active vaccine, he did not receive RIG, which is life-saving in individuals with severe exposures. Administration of human or equine RIG (or recently available monoclonal antibodies) could have possibly prevented rabies in this case.

The Case Continued…

After admission, the patient developed autonomic instability evidenced by increased perspiration and significant variability in heart rate and blood pressure. He developed dysphagia and respiratory distress requiring mechanical ventilation on the third day after hospitalization. His saliva sample collected at admission was positive for rabies viral RNA by RT-PCR; a CSF sample was negative. The patient died because of a sudden cardiac arrest on the fifth day of hospitalization (9 days post-onset of symptoms).

SUMMARY BOX

Rabies

Rabies is a progressive, fatal encephalomyelitis caused by viruses of the *Lyssavirus* genus (Order *Mononegavirales*, Family *Rhabdoviridae*). Rabies lyssavirus (RABV), the prototype virus of the *Lyssavirus* genus, is the most common causative agent of rabies, usually transmitted through the bite of infected mammals, mostly dogs. About 61 000 human global deaths occur because of rabies annually, mostly in Asia and Africa.

The incubation period is usually 20 to 90 days, but may vary. Two distinct clinical forms of rabies are recognized: Encephalitic ("furious") and paralytic ("dumb"). The encephalitic form rarely poses diagnostic difficulties because of the classical clinical features like hydrophobia, aerophobia, agitation and

TABLE 91.2 Tests for Laboratory Diagnosis of Rabies

	Sample(s)	Test(s)	Detection	Sensitivity	Remarks
Ante-mortem Diagnosis*	Saliva	RT-PCR	Viral nucleic acid	Moderate to high sensitivity	Testing serial/pooled samples recommended to increase sensitivity
	Nuchal skin biopsy	RT-PCR	Viral nucleic acid	Moderate to high sensitivity	Full thickness biopsy and adequate hair follicles required
	CSF, Urine	RT-PCR	Viral nucleic acid	Low sensitivity	
	CSF, Serum	RFFIT, FAVN, ELISA	Neutralizing Antibodies (RFFIT, FAVN); Antibodies against viral glycoprotein (ELISA)	Low sensitivity in first week of illness; rises with increased duration of survival (>90% by 2 weeks)	Presence of antibodies in CSF (irrespective of prior vaccination status) and serum (in previously unvaccinated cases) diagnostic of rabies
Post-mortem Diagnosis**	Brain tissue	dFA, RT-PCR	Viral antigen	High sensitivity (nearly 100%)	Gold standard for laboratory confirmation (dFA)

RT-PCR: Reverse transcriptase polymerase chain reaction; RFFIT: Rapid fluorescent focus inhibition test; FAVN: Fluorescent antibody virus neutralization; dFA: Direct fluorescent antibody

*A positive test confirms rabies; negative test results cannot rule out a diagnosis of rabies completely

**A positive test on brain tissue confirms rabies; negative test rules out rabies

autonomic dysfunction; however, paralytic rabies may clinically mimic Guillain Barré syndrome (GBS), post-vaccination encephalomyelitis and other conditions (Table 91.1) posing a challenge in diagnosis and management. Fever at onset, paraesthesia in the bitten limb, rapid progression, quadriparesis with predominant involvement of proximal muscles, bowel and bladder involvement, percussion myoedema, presence of hydrophobia/aerophobia and CSF pleocytosis seen in paralytic rabies can help differentiate it from GBS. Post-vaccination complications historically observed with nerve tissue vaccines used in the past are rarely seen with the currently used rabies vaccines derived from tissue culture or embryonated eggs. High titres of neutralizing antibodies in CSF and serum and predominant involvement of grey matter in brain and spinal cord on neuroimaging in paralytic rabies can help distinguish it from post-vaccination neurological complications.
Nerve conduction studies (an axonal neuropathy supports rabies), neuroimaging and laboratory tests (Table 91.2) can aid in the diagnosis.

Currently, there is no specific antiviral therapy of proven efficacy for rabies. Management consists of symptomatic treatment and supportive care. Prognosis is dismal in both forms of rabies, resulting in death within one to 2 weeks of symptom onset. Survival from rabies is extremely rare, though critical care can reportedly prolong survival by a few weeks or months in some cases.

This fatal disease can be prevented in most cases with appropriate PEP after exposure. Pre-exposure prophylaxis is recommended in individuals at high risk, including travellers to rabies-endemic countries.

Further Reading

1. Warell MJ. *Rabies*. In: Farrar J, editor. Manson's Tropical Diseases. 23rd ed. London: Elsevier; 2013 [chapter 52].
2. Willoughby RE. Jr. Rabies: rare human infection - common questions. Infect Dis Clin North Am 2015;29(4):637–50.
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4. World Health Organization. WHO Expert Consultation on Rabies: Third report. World Health Organization Technical Report Series 1012. Geneva: WHO; 2018.
5. Fooks AR, Cliquet F, Finke S, et al. Rabies. Nat Rev Dis Primers 2017;3:17091.