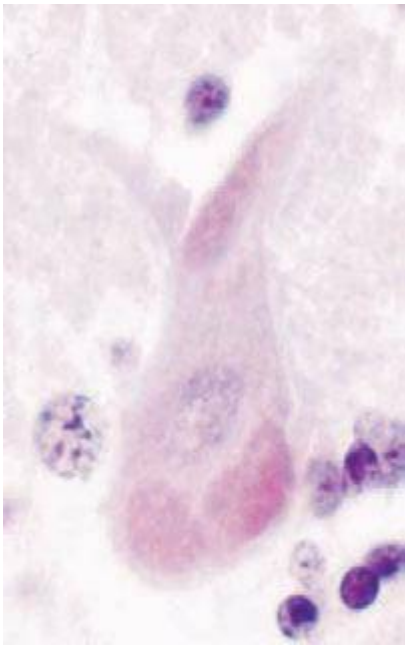

**FIGURE 232-3 Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell** from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. *(From AC Jackson, E Lopez-Corella: N Engl J Med 335:568, 1996. © Massachusetts Medical Society.)*

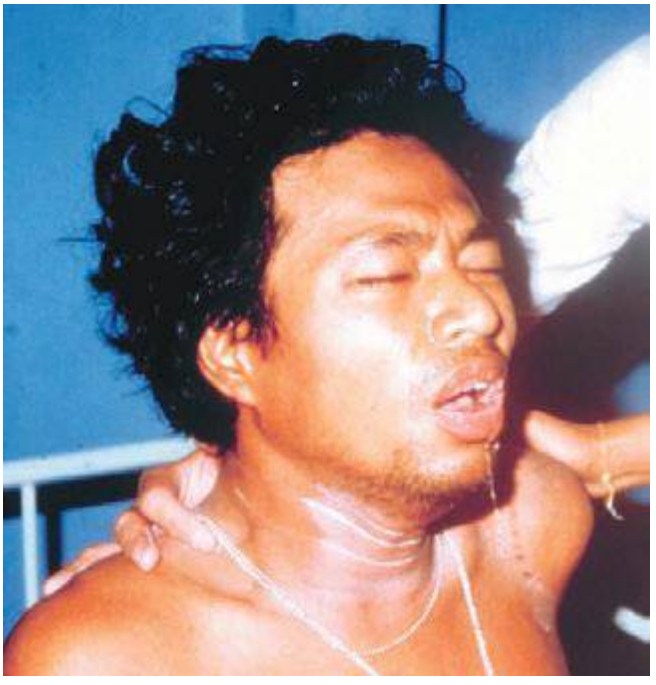

**FIGURE 232-4 Hydrophobic spasm of inspiratory muscles associated with terror** in a patient with encephalitic (furious) rabies who is attempting to swallow water. *(Copyright DA Warrell, Oxford, UK; with permission.)*



weakness. Sphincter involvement is common, sensory involvement is usually mild, and these cases are commonly misdiagnosed as Guillain-Barré syndrome. Patients with paralytic rabies generally survive a few days longer than those with encephalitic rabies, but multiple-organ failure nevertheless ensues.

## LABORATORY INVESTIGATIONS

Most routine laboratory tests in rabies yield normal results or show nonspecific abnormalities. Complete blood counts are usually normal. Examination of cerebrospinal fluid (CSF) often reveals mild mononuclear cell pleocytosis with a mildly elevated protein level. Severe pleocytosis (>1000 white cells/μL) is unusual and should prompt a search for an alternative diagnosis. CT head scans are usually normal in rabies. MRI brain scans may show signal abnormalities in the brainstem or other gray-matter areas, but these findings are variable and nonspecific. Electroencephalograms show only nonspecific abnormalities. Of course, important tests in suspected cases of rabies include those that may identify an alternative, potentially treatable diagnosis (see "Differential Diagnosis," below).

**TABLE 232-1 CLINICAL STAGES OF RABIES**

| Phase | Typical Duration | Symptoms and Signs |
|---|---|---|
| Incubation period | 20–90 days | None |
| Prodrome | 2–10 days | Fever, malaise, anorexia, nausea, vomiting; paresthesias, pain, or pruritus at the wound site |
| Acute neurologic disease | | |
| Encephalitic (80%) | 2–7 days | Anxiety, agitation, hyperactivity, bizarre behavior, hallucinations, autonomic dysfunction, hydrophobia |
| Paralytic (20%) | 2–10 days | Flaccid paralysis in limb(s) progressing to quadriparesis with facial paralysis |
| Coma, death[a] | 0–14 days | |

[a]Recovery is rare.

***Source:*** MAW Hattwick: Rabies virus, in *Principles and Practice of Infectious Diseases,* GL Mandell et al (eds). New York, Wiley, 1979, pp 1217–1228. Adapted with permission from Elsevier.

## DIAGNOSIS

In North America, a diagnosis of rabies often is not considered until relatively late in the clinical course, even with a typical clinical presentation. This diagnosis should be considered in patients presenting with acute atypical encephalitis or acute flaccid paralysis, including those in whom Guillain-Barré syndrome is suspected. The absence of an animal-bite history is common in North America. The lack of hydrophobia is not unusual in rabies. Once rabies is suspected, rabies-specific laboratory tests should be performed to confirm the diagnosis. Diagnostically useful specimens include serum, CSF, fresh saliva, skin biopsy samples from the neck, and brain tissue (rarely obtained before death). Because skin biopsy relies on the demonstration of rabies virus antigen in cutaneous nerves at the base of hair follicles, samples are usually taken from hairy skin at the nape of the neck. Corneal impression smears are of low diagnostic yield and are generally not performed. Negative antemortem rabies-specific laboratory tests never exclude a diagnosis of rabies, and tests may need to be repeated after an interval for diagnostic confirmation.

**Rabies Virus–Specific Antibodies** In a previously unimmunized patient, serum neutralizing antibodies to rabies virus are diagnostic. However, because rabies virus infects immunologically privileged neuronal tissues, serum antibodies may not develop until late in the disease. Antibodies may be detected within a few days after the onset of symptoms, but some patients die without detectable antibodies. The presence of rabies virus–specific antibodies in the CSF suggests rabies encephalitis, regardless of immunization status. A diagnosis of rabies is questionable in patients who recover from rabies without developing serum neutralizing antibodies to rabies virus.

**RT-PCR Amplification** Detection of rabies virus RNA by RT-PCR is highly sensitive and specific. This technique can detect virus in fresh saliva samples, skin, CSF, and brain tissues. In addition, RT-PCR with genetic sequencing can distinguish among rabies virus variants, permitting identification of the probable source of an infection.

**Direct Fluorescent Antibody Testing** Direct fluorescent antibody (DFA) testing with rabies virus antibodies conjugated to fluorescent dyes is highly sensitive and specific and can be performed quickly and applied to skin biopsies and brain tissue. In skin biopsies, rabies virus antigen may be detected in cutaneous nerves at the base of hair follicles.