

Lymphocytic Choriomeningitis Virus: Reemerging Central Nervous System Pathogen

Leslie L. Barton, MD, and N. Joanne Hyndman, MD

ABSTRACT. Lymphocytic choriomeningitis virus (LCMV), a human zoonosis caused by a rodent-borne arenavirus, has been associated with both postnatal and intrauterine human disease. Infection in man is acquired after inhalation, ingestion, or direct contact with virus found in the urine, feces, and saliva of infected mice, hamsters, and guinea pigs. Congenital LCMV infection is a significant, often unrecognized cause of chorioretinitis, hydrocephalus, microcephaly or macrocephaly, and mental retardation. Acquired LCMV infection, asymptomatic in approximately one third of individuals, is productive of central nervous system manifestations in one half of the remaining cases. Aseptic meningitis or meningoencephalitis are the predominant syndromes, although transverse myelitis, a Guillain-Barré-type syndrome, as well as transient and permanent acquired hydrocephalus have also been reported. Fatalities are rare. We report a patient with meningoencephalitis attributable to LCMV and discuss the spectrum of central nervous system disease, newer diagnostic modalities, and preventive strategies. *Pediatrics* 2000;105(3). URL: <http://www.pediatrics.org/cgi/content/full/105/3/e35>; *lymphocytic choriomeningitis virus, aseptic meningitis, meningoencephalitis, zoonosis, hydrocephalus, arenavirus.*

ABBREVIATIONS. LCMV, lymphocytic choriomeningitis virus; CSF, cerebrospinal fluid; IFA, immunofluorescent antibody; IgM, immunoglobulin M; IgG, immunoglobulin G.

Lymphocytic choriomeningitis virus (LCMV), a rodent-borne arenavirus, has recently been recognized as a human teratogenic pathogen.¹⁻⁴ The devastating sequelae of congenital infection include chorioretinitis, hydrocephalus, microcephaly or macrocephaly, intracranial calcifications, mental retardation, and seizures. Acquired LCMV disease, however, has received relatively scant attention.^{1,5} We report a patient with meningoencephalitis caused by LCMV to increase physician awareness of this potentially preventable infection. This case also illustrates the diagnostic conundrum LCMV infection may pose, when the initial history of illness does not elicit rodent exposure.

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CASE REPORT

A 17-year-old girl was referred for admission to University Medical Center on December 26, 1998 with a 1-week history of headache, dizziness, nausea, vomiting, tactile fever, and cerebrospinal fluid (CSF) pleocytosis noted on lumbar puncture. The patient had ingested nonsteroidal antiinflammatory drugs with only temporary relief. She denied concurrent upper respiratory symptoms, diarrhea, or rash. At the referring institution a complete blood count, serum electrolytes, and lumbar puncture were performed. Hemoglobin was 14.2 g/dL; hematocrit was 40.2%; and white blood cell count was 16 500/mm³ with 84% polymorphonuclear cells, 9% lymphocytes, and 7% monocytes; platelet count was 364 000/mm³. CSF contained 1 red blood cell and 9760 white blood cells/mm³ (100% mononuclear cells). CSF protein was 231 mg/dL; glucose was 58 mg/dL; and serum glucose was 137 mg/dL. No organisms were seen on Gram stain. The patient received 1 g of ceftriaxone before transport. On admission to University Medical Center her temperature was 37.5°C, heart rate 80 beats per minute, respiratory rate 16 per minute, and blood pressure 108/68 mm Hg. She had normal fundoscopic and neurologic examinations with the exception of mild hyperreflexia. Her neck was supple with full range of motion.

Additional questioning of the patient revealed significant exposure to cats, dogs, and mice at home. Viral cultures of nasopharyngeal, oropharyngeal, and rectal swabs and CSF; *Coccidioides immitis*, Epstein-Barr virus, LCMV, mycoplasma, and *Bartonella henselae* serologies were obtained. Intradermal tuberculin skin test was placed. After 48 hours of hospitalization, the patient's symptoms had resolved; CSF culture and tuberculin test results were negative. She was discharged from the hospital with a presumptive diagnosis of viral meningitis.

The patient was seen again ~3 weeks after discharge. She had no headache but had persistent emesis, decreased food intake and a 2-lb weight loss. Additional historical data included significant preillness exposure to mouse droppings, via inhalation, and/or direct contact, during a high school kitchen cleanup. Physical examination was remarkable only for persistent hyperreflexia and moderate nystagmus on lateral gaze. At that time, all laboratory test results, including bacterial, mycobacterial, fungal cultures, and all serologies obtained during hospitalization, were negative. However, LCMV antibody had been determined by complement fixation. Therefore, the LCMV serology was repeated by immunofluorescent antibody (IFA) technique. Repeat mycoplasma serologies and a magnetic resonance imaging study of the head were also performed and were negative. LCMV IFA was positive with immunoglobulin M (IgM) >1:20 and an immunoglobulin G (IgG) ≥1:256. One month later, repeat LCMV IgM was <1:20 and IgG was unchanged at ≥1:256. Of note, 2 of 5 mice subsequently trapped at the high school were LCMV antibody positive.

DISCUSSION

LCMV disease is a zoonosis acquired by contact with infected mice, hamsters, guinea pigs, and their excreta. Postnatal human infection is asymptomatic in approximately one third of patients.⁶ Approximately one half of the remaining cases develop aseptic meningitis or meningoencephalitis, although transverse myelitis and the Guillain-Barré syndrome have also been reported.⁷ Fatalities have been rare, as have been long-term sequelae, which have included

transient and permanent acquired hydrocephalus and deafness.^{1,8} Neuropathologic studies of human and animal LCMV infection have demonstrated mononuclear cell infiltrates in meninges, choroid plexus, and ependyma.^{1,9,10} These observations may explain the obstructive hydrocephalus observed in both congenital and acquired LCMV infections with central nervous system involvement.

We suggest that LCMV infection of the central nervous system is underdiagnosed. Between 1941 and 1958 in a study of hospitalized patients with aseptic meningitis, nearly 10% were attributable to LCMV, and it was the most common cause during the winter months, presumably attributable to movement of mice indoors.¹¹ There are no pathognomonic signs, symptoms, or laboratory abnormalities in this infection. Fever, headache, nausea, vomiting, and occasional photophobia are prominent symptoms. As in our patient, significant CSF pleocytocytosis may occur, which is unusual in other viral infections. CSF white blood cell counts have ranged from <30 to >3000, generally predominantly mononuclear cells.¹² Normal to slightly decreased CSF glucose and slightly to moderately increased protein concentrations have been noted. CSF eosinophilia has been reported in 1 infected child.¹³

This case also illustrates the importance of using appropriate and sensitive diagnostic serologic tests. The complement fixation test for LCMV, although widely available, is insensitive^{14,15} and proved negative in our patient. Because of the strong suspicion of LCMV infection, repeat testing using the more sensitive IFA test was performed and revealed late acute or early convalescent LCMV infection with both measurable IgM and IgG antibody in the first serum specimen and only IgG antibody in the second (convalescent) specimen. A sensitive, enzyme-linked immunosorbent assay, which measures LCMV IgM and IgG is also available and performed at the Centers for Disease Control and Prevention.²

LCMV infections may be prevented by public education of the need to avoid contact with potentially infected rodents and their excreta. After diagnosis of LCMV meningoencephalitis in our patient, Health Department and school personnel were notified. Mousetraps were placed in and around the high

school and resulted in rapid abatement of the rodent infestation problem.

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REFERENCES

1. Larsen PD, Chartrand SA, Tomashek KM, Hauser LG, Ksiazek TG. Hydrocephalus complicating lymphocytic choriomeningitis virus infection. *Pediatr Infect Dis J*. 1993;12:528-531
2. Barton LL, Budd SC, Morfitt WS, et al. Congenital lymphocytic choriomeningitis virus infection in twins. *Pediatr Infect Dis J*. 1993;12:942-946
3. Wright R, Johnson D, Neumann M, et al. Congenital lymphocytic choriomeningitis virus syndrome: a disease that mimics congenital toxoplasmosis or cytomegalovirus infection. *Pediatrics*. 1997;100(1). URL: <http://www.pediatrics.org/cgi/content/full/100/1/e9>
4. Barton LL, Peters CJ, Ksiazek TG. Lymphocytic choriomeningitis virus: an unrecognized teratogenic pathogen. *Emerg Infect Dis*. 1995;1:152-153
5. Brouqui P, Rousseau MC, Saron MF, Bourgeade A. Meningitis due to lymphocytic choriomeningitis virus: four cases in France. *Clin Infect Dis*. 1995;20:1082-1083
6. Deibel R, Woodall JP, Decher WJ, Schryver GD. Lymphocytic choriomeningitis virus in man: serologic evidence of association with pet hamsters. *JAMA*. 1975;232:501-504
7. Lehmann-Grube F. Diseases of the nervous system caused by lymphocytic choriomeningitis virus and other arenaviruses. In: *Handbook of Clinical Neurology*. New York, NY: Elsevier; 1989:355-381
8. Tindall GT, Gladstone LA. Hydrocephalus as a sequel to lymphocytic choriomeningitis. *Neurology*. 1957;7:516-518
9. Sheinbergas MM, Pmashekas RS, Pikelite RL, et al. Clinical and pathomorphological data on hydrocephalus caused by prenatal infection by the lymphocytic choriomeningitis virus. *Zh Nevropatol Psikhiatr*. 1977;77:1004-1007
10. Ackermann R, Kalter SS, Heberling RL, McCullough B, Eichberg J, Rodriquez AR. Fetal infection of the baboon (*Papio cynocephalus*) with lymphocytic choriomeningitis virus. *Arch Virol*. 1979;60:311-323
11. Meyer HM, Johnson RT, Crawford IP, Dascomb HE, Rogers NG. Central nervous system syndromes of "viral" etiology: a study of 713 cases. *Am J Med*. 1960;29:334-347
12. Green WR, Sweet LK, Prichard RW. Acute lymphocytic choriomeningitis: a study of twenty-one cases. *J Pediatr*. 1949;35:688-701
13. Chesney PJ, Katcher MJ, Nelson DB, Horowitz SD. CSF eosinophilia and chronic lymphocytic choriomeningitis virus meningitis. *J Pediatr*. 1979;750-752
14. Lewis VJ, Walter PD, Thacker WL, Winkler WG. Comparison of three tests for the serologic diagnosis of lymphocytic choriomeningitis virus infection. *J Clin Microbiol*. 1975;2:193-197
15. Lehmann-Grube F, Kallay M, Ibscher B, Schwartz R. Serologic diagnosis of human infections with lymphocytic choriomeningitis virus: comparative evaluation of seven methods. *J Med Virol*. 1979;4:125-136

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