An Unusual Case of Rabies Encephalitis

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ABSTRACT: Human rabies encephalitis is rare in Canada, with only five cases reported in the past 30 years. The first and only patient who contracted rabies encephalitis in British Columbia died in 2003. Here we provide the first detailed clinical and pathological description of that case, which had several unusual features, including preexisting immunosuppression, paralytic presentation, prolonged survival, focal lesions on neuroimaging and severe neuropathology with focal necrosis, intense inflammation, and abundant viral inclusion bodies.

RÉSUMÉ: Un cas inusité d'encéphalite rabique. L'encéphalite rabique est rare au Canada. Seulement 5 observations de cette maladie ont été rapportées au cours des 30 dernières années. Le premier de ces patients et le seul en Colombie Britannique, est mort en 2003. Nous rapportons ici la première description clinique et anatomopathologique concernant ce patient. Il présentait plusieurs caractéristiques inusitées dont une immunosuppression préexistante, des symptômes initiaux de paralysie, une survie prolongée, des lésions focales à la neuroimagerie et une neuropathologie sévère avec nécrose focale, inflammation importante et de nombreux corps d'inclusion viraux.

Keywords: Rabies, Encephalitis

doi:10.1017/cjn.2016.287 Can J Neurol Sci. 2016; 43: 852-855

Human rabies infection is estimated to be responsible for more than 50,000 deaths per year worldwide (reviewed in Jackson[1]). Most cases occur in India and other parts of Asia and Africa, and are usually the result of dog bites. Vaccination of domestic animals results in few cases in Europe and North America, where most are due to contact with wild animals.

Rabies is an enveloped RNA virus of the family Rhabdovirus, genus *Lyssavirus*. Following inoculation, initial replication occurs locally in the subcutaneous tissue or muscle, with subsequent spread to the peripheral nervous system and then the central nervous system. Following a variable period of incubation, a flulike prodrome precedes the acute phase that may be encephalitic (in 70%-80%) or paralytic (in 20%-30%). Coma leading to death represents the terminal phase. The mean survival following onset of the acute phase is 1 to 2 weeks. Antemortem diagnosis may be made by identifying rabies antibodies in patient serum or cerebrospinal fluid (CSF); detecting viral RNA in saliva, CSF, or skin; or by viral immunofluorescence on corneal smears or skin biopsies. Neuroimaging is usually negative.

There have been only five cases of human rabies reported in Canada in the past 30 years.[2-7] The patient described here died in 2003 and a brief report, focusing on the public health measures, was published shortly thereafter.[4] However, the rarity of this disease in Canada and the unusual clinical and pathological features makes more detailed documentation of this case warranted.

Case Report

Clinical History

This 52-year-old man had a long history of bipolar affective disorder. Kidney failure resulting from lithium toxicity required renal transplant in 2000 and ongoing immunosuppression with tacrolimus, sirolimus, and prednisone. He presented in January 2003, to his regional hospital, with 2 days of progressive left arm weakness. Examination demonstrated a flaccid left arm, weak right arm, and absent deep tendon reflexes in both arms. Mental status and vital signs were normal, but he had mild respiratory insufficiency. His weakness progressed rapidly; by day 3, he had no voluntary movement or deep tendon reflexes and required intubation. Brain computed tomography and magnetic resonance imaging scans at that time were normal. CSF protein was 568 mg/dl, with 23 white blood cells/mm^3 and normal glucose. HIV 1 and 2 serology were negative. Nerve conduction studies showed multiple absent compound motor action potentials and sensory nerve action potentials and absent F-waves, felt to be consistent with severe axonal Guillain-Barre syndrome. A 5-day course of intravenous immunoglobulin (400 mg/kg) did not lead to improvement and he was transferred to a tertiary care hospital. On day 10, the patient would open his eyes to loud commands, had normal pupillary and corneal responses, but was ophthalmoplegic and tetraplegic with no tendon reflexes. Five days of plasmapheresis was not effective. By day 16, there were no brainstem or motor responses and electroencephalograph revealed a burst suppression pattern with silent periods of 1 to 2 seconds. Treatment with ganciclovir was initiated on day 18. Magnetic resonance imaging on day 21 showed multifocal T2 hyperintense lesions in cerebral gray and white matter (Figure 1). Polymerase

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Received October 19, 2015. Revised February 16, 2016. Date of Acceptance March 11, 2016.

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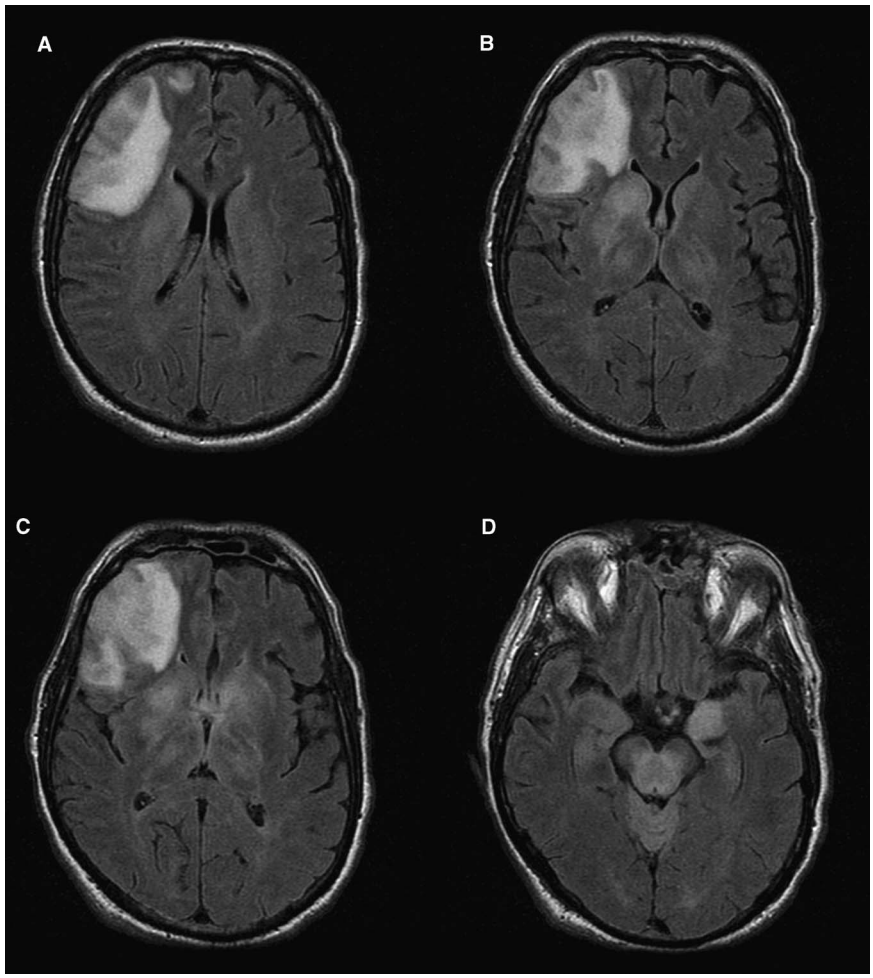

Figure 1: *Axial T2 fluid-attenuated inversion recovery images on day 21 showing multiple areas of T2 hyperintensity including a large right frontal lesion involving both gray and white matter (A-C); lesions involving right caudate head, bilateral lentiform nuclei, and thalami (B, C); and left uncus, both hippocampi, midbrain tegmentum, and the cerebellar vermis (D).*

chain reaction studies performed on the original CSF sample for herpes simplex, varicella zoster, Epstein Barr, and cytomegalovirus came back negative. Repeat CSF showed protein of 3044 mg/dl, 650 white blood cells/mm^3, and normal glucose. On day 22, his electroencephalograph showed a continuous burst suppression pattern; brainstem auditory and somatosensory-evoked potentials failed to elicit any response and supportive measures were discontinued. He died of respiratory arrest 24 days after initial presentation.

Additional history obtained just before his death indicated that the patient had spent much time in the local forest, often drank stream water, and had recently discovered an abandoned cabin that was infested with mice. There was no history of foreign travel or animal bite.

Pathological Findings

The postmortem brain weighed 1580 grams and appeared mildly swollen. There were focal areas of tissue softening and discoloration in the right frontal lobe, primarily involving the subcortical white matter (Figure 2A). Smaller, more ill-defined areas of tissue discoloration were seen in many other regions. Histology showed the right frontal lesions to consist of partially cystic, confluent areas of necrotic cerebral white matter composed of acellular proteinaceous material and nuclear debris, surrounded by a zone of intense acute and subacute inflammation (Figure 2B). Meningoencephalitis with acute and chronic inflammation, neuronal loss, and reactive changes (Figure 2C) were present in all areas of the central nervous system, including the neocortex, limbic cortex, basal ganglia, thalamus, brainstem, cerebellum, and spinal cord. The majority of surviving neurons contained one or more well-defined eosinophilic cytoplasmic inclusion bodies, consistent in morphology with Negri bodies (Figure 2D, E). There was focal inflammation of the spinal nerve roots, dorsal root ganglia, and peripheral nerves. The histologic diagnosis of rabies meningoencephalomyelitis was confirmed by direct fluorescent antibody testing and immunohistochemistry on postmortem brain tissue (Figure 2F), performed at the animal health laboratory of the Canadian Food Inspection Agency in Ottawa. Reverse transcriptase polymerase chain reaction identified the viral strain as that associated with little brown bats in western Canada.

https://doi.org/10.1017/cjn.2016.287 Published online by Cambridge University Press

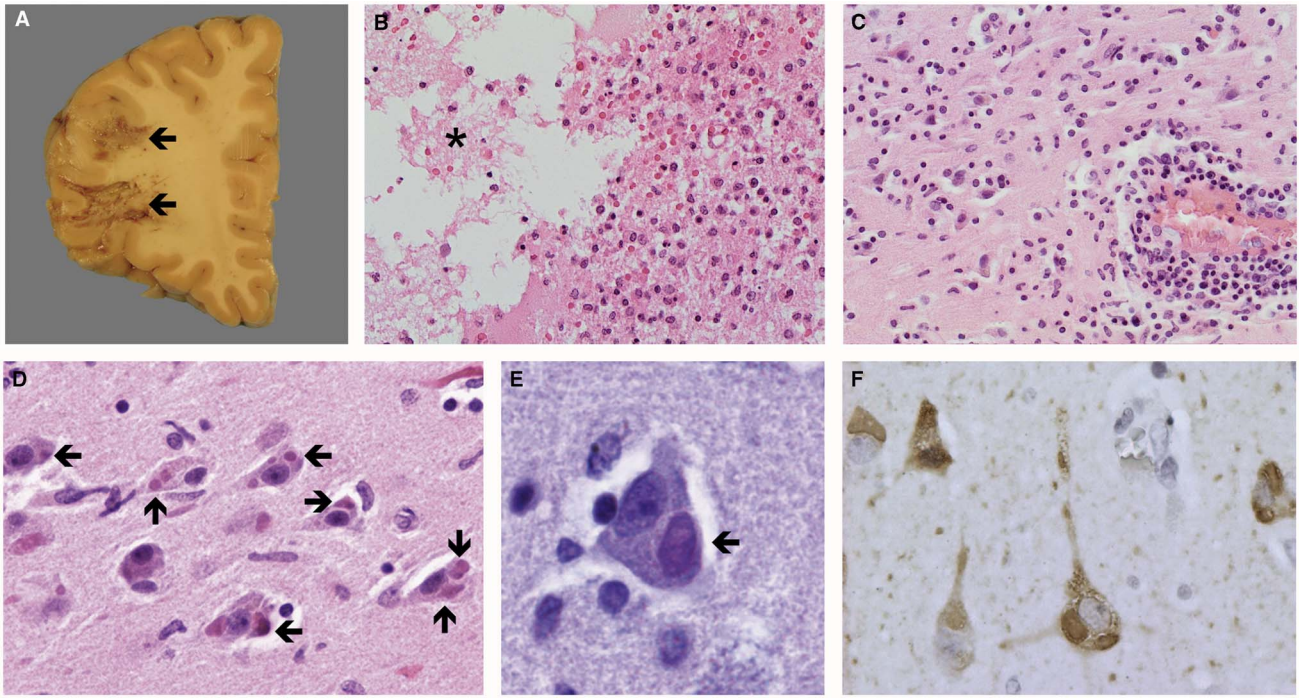

Figure 2: *Postmortem pathological findings. Coronal sections of the formalin-fixed brain showing focal areas of subacute necrosis in the right frontal lobe (arrows, A), histologically characterized by partially cystic areas of necrotic cerebral white matter (*) surrounded by a zone of intense acute and subacute inflammation (B, hematoxylin and eosin [HE] stain). Encephalitis with acute and chronic inflammatory infiltrates, reactive astrogliosis, microglial proliferation, and neuronal loss was present in the cerebral hemispheres (C, HE stain) and in all other regions of the central and peripheral nervous system examined. Eosinophilic neuronal cytoplasmic inclusion bodies, consistent with Negri bodies, were numerous in all brain regions (arrows, D and E, HE stain) including the cerebral cortex (D) and basal ganglia (E). Immunohistochemistry with a rabies-specific antibody demonstrated numerous neuronal inclusion bodies (F, cerebral cortex).*

Public Health Measures

The diagnosis of rabies was first made by the neuropathologist, 4 weeks after the patient's death, with confirmation by immunofluorescence 48 hours later. A postexposure prophylaxis program was initiated the following day with 440 health care workers at two hospitals, 12 community contacts, and two household contacts treated with rabies postexposure prophylaxis immunization.[4]

Discussion

There have been only 25 cases of human rabies reported in Canada since 1925, with most occurring in Quebec (12) and Ontario (7).[2-7] The patient reported here is the first and only case contracted in British Columbia, although another individual died of rabies in British Columbia following exposure while hunting in Alberta.[7] Our case demonstrated several unusual clinical and pathological features that are worth emphasizing.

A diagnosis of rabies was not considered in our patient before his death. This is not uncommon, with antemortem diagnosis achieved in only 20/32 (63%) cases confirmed in the United States from 1980 through 1996.[8] Factors that contribute to missed diagnosis include the rarity of the disorder in North America and the frequent lack of a history of animal exposure (present in only 22%), particularly in cases resulting from bats.[8] A further complication in our patient was that he presented with the less common paralytic form of disease. Consideration of other treatable causes of paralysis resulted in our patient's survival being artificially prolonged to 3.5 weeks, twice the normal range.

The neuropathological features of rabies meningoencephalitis are variable and do not correlate well with the clinical presentation. The brain is usually grossly normal. Histopathological features include inflammation, neuronal loss, neuronal cytoplasmic inclusions (Negri bodies and lyssa bodies), and peripheral neuropathy. There is often a striking disparity between the apparent viral burden, the degree of inflammation, and neuronal loss. In general, cases with short survival are more likely to have intense inflammation despite relatively few viral inclusions, supporting the notion that the host's antiviral immune response contributes to rabies virus spread and pathogenesis.[9] Prolonged survival is usually the result of artificial ventilatory support, and these cases tend to have more abundant viral inclusions. Focal or diffuse tissue necrosis is a rare feature that has usually been reported in cases of prolonged survival. In some cases, necrosis may be the result of brain swelling and hypoxia; however, in the case reported by Dolman et al, oxygenation had been well-maintained, there was minimal brain swelling, and the anatomical pattern of necrosis matched the topographic predilection of the virus.[7] In our case, the preexisting and subsequent immunosuppressive therapies may have allowed for more extensive viral spread, but did not prevent a florid inflammatory response. A similar combination of diffuse inflammation and abundant Negri bodies has been reported in cases of rabies following organ transplant and immunosuppressive therapy.[10] The combination of

https://doi.org/10.1017/cjn.2016.287 Published online by Cambridge University Press

high viral burden, intense immune response, and artificially prolonged survival were likely responsible for the unusual findings of focal lesions on neuroimaging and necrosis found at autopsy.

There are different strains of rabies virus, each primarily associated with a single mammalian species. Of the 26 cases of human rabies acquired in the United States between 1990 and 2000, 24 (92%) were the result of various bat strains.[11] The number of human infections associated with each strain is influenced by the rate of endemic infection within different bat populations, variation in the degree of infectivity of each viral strain, and factors that determine the likelihood of human contact. Big brown and little brown bats are among the most common bat species in North America with a high frequency human contact; however, these species have some of the lowest levels of infection (5.8% and 1.7%, respectively).[11] Of the eight cases of human rabies in Canada since 1970 (including this one), seven were due to bats.[2-6] In British Columbia, rabies is endemic only in bats, with an estimate of 1% of all bats infected.[4]

In summary, this is the only case of human rabies contracted in British Columbia. Incorrect clinical diagnosis led to artificially prolonged survival and immunosuppressant therapy that, combined with the patient's preexisting immunosuppression, may have contributed to unusual features, including the paralytic presentation, focal lesions on neuroimaging and severe neuropathology with focal necrosis, intense inflammation, and abundant viral inclusion bodies.

Acknowledgments

Diagnostic rabies immunofluorescence and immunohistochemistry were performed by Alexander Wandeler and genotyping was performed by Susan Nadin-Davis of the Centre of Expertise for Rabies, Canadian Food Inspection Agency.

Disclosures

None of the authors have anything to disclose.

Statement of Authorship

The manuscript was prepared by GW and IRM with clinical information provided by BT, description of the radiology from DG, and neuropathological findings contributed by GRWM and IRAM.

References

1. Jackson AC. Update on rabies. Curr Opin Neurol. 2002;15:327-31.
2. Centers for Disease Control and Prevention. Human rabies—Québec, Canada, 2000. MMWR Morb Mortal Wkly Rep. 2000;49:1115-6.
3. McDermid RC, Saxinger L, Lee B, et al. Human rabies encephalitis following bat exposure: failure of therapeutic coma. Can Med Assoc J. 2008;178:557-61.
4. Parker R, McKay D, Hawes C, et al. Human rabies, British Columbia-January 2003. Can Commun Dis Rep. 2003;29:137-8.
5. Varughese P. Human rabies in Canada—1924-2000. Can Commun Dis Rep. 2000;26:210-1.
6. Wilcox ME, Poutanen SM, Krajden S, Agid R, Kiehl TR, Tang-Wai DF. A case of rabies encephalitis: new dog, old tricks. Neurology. 2014;82:1101.
7. Dolman CL, Charlton KM. Massive necrosis of the brain in rabies. Can J Neurol Sci. 1987;14:162-5.
8. Noah DL, Drenzek CL, Smith JS, et al. Epidemiology of human rabies in the United States, 1980 to 1996. Ann Intern Med. 1998;128:922-30.
9. Hooper DC. The role of immune responses in the pathogenesis of rabies. J Neurovirol. 2005;11:88-92.
10. Srinivasan A, Burton EC, Kuehnert MJ, et al. Transmission of rabies virus from an organ donor to four transplant recipients. N Engl J Med. 2005;352:1103-11.
11. Mondul AM, Krebs JW, Childs JE. Trends in national surveillance for rabies among bats in the United States (1993-2000). J Am Med Assoc. 1993;222:633-9.

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