A Fatal Case of Coxsackievirus B4 Meningoencephalitis

Bruce C. Cree, MD, PhD; Gary L. Bernardini, MD, PhD; Arthur P. Hays, MD; Gina Lowe, MD

Background: Coxsackieviruses and echoviruses are common causes of aseptic meningitis, but they rarely cause life-threatening illness. We report a fatal case of coxsackievirus B4 meningoencephalitis in a woman who developed extrapyramidal symptoms suggestive of encephalitis lethargica. The exact causative agent of encephalitis lethargica has rarely been found, but most cases of the syndrome are assumed to be of viral origin.

Case Description: A 33-year-old woman previously treated with methylprednisolone and cyclophosphamide for Henoch-Schönlein purpura was transferred from a referring hospital because of sore throat, fever, and chills. Her neurologic findings progressed from headache with mild photophobia to lethargy, cogwheeling, increased tone in all 4 limbs, and brisk reflexes. The patient was diagnosed as having coxsackievirus B4 meningoencephalitis and, despite treatment with the experimental antiviral agent pleconaril, died of an overwhelming central nervous system infection and myocarditis. Magnetic resonance imaging showed focal hyperintense lesions in the substantia nigra that corresponded to the location of pathological changes seen at autopsy.

Conclusions: This patient had a fulminant coxsackievirus B4 viral meningoencephalitis with a clinical pattern reminiscent of encephalitis lethargica and striking focal abnormalities in the substantia nigra identified on magnetic resonance imaging. The magnetic resonance imaging findings correlated with pathological changes identified at autopsy that were similar to the pathological findings observed in patients with encephalitis lethargica and postencephalitic parkinsonism. It is likely that the patient's immunocompromised state led to an overwhelming infection from an otherwise relatively innocuous viral infection.

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Approximately 20,000 cases of acute encephalitis are reported each year in the United States. In most cases, the causative infectious agent is viral, including Enteroviridae (eg, echovirus or coxsackievirus), arbovirus (eg, West Nile, eastern or western equine, St Louis, Venezuelan equine, California, or LaCrosse virus), Herpesviridae (eg, herpesvirus type 1 or 2, varicella-zoster virus, Epstein-Barr virus, and cytomegalovirus), and parovirus, and can be identified from the cerebrospinal fluid (CSF) and/or blood. However, determination of the exact cause can be difficult, often requiring repeated CSF sampling and polymerase chain reaction amplification of the CSF. Abnormalities within the brain parenchyma (eg, medial temporal lobes or brainstem) seen on magnetic resonance (MR) imaging with T2- or T1-weighted images after gadolinium contrast injection can help to establish the diagnosis.

Coxsackievirus and echovirus are frequent causes of aseptic meningitis, particularly in children, but are rarely life threatening. We report a fatal case of meningoencephalitis and inflammatory myocarditis caused by coxsackievirus B4 likely owing to susceptibility in an individual with a pharmacologically induced state of immunosuppression.

A 33-year-old woman was admitted to a community hospital because of 1 week of malaise, sore throat, subjective fever, chills, bilateral ear pain, and joint pain in her hands and feet. The patient had a history of Henoch-Schönlein purpura, juvenile rheumatoid arthritis treated with methylprednisolone and cyclophosphamide, and required hemodialysis for IgA nephropathy. On presentation, her temperature was 39.8°C and a 2/6 systolic murmur was heard at the left sternal border. Results of general physical and neurologic examination were normal. Routine complete blood cell count showed a white blood cell (WBC) count of $1.7 \times 10^9/\mu L$, with a dif-

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Cerebrospinal Fluid Analysis

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<td>ND</td>
<td>ND</td>
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<td>WBC count, cells (\times 10^3/\mu L)</td>
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<td>Glucose, mg/dL</td>
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Abbreviations: ND, not determined; RBC, red blood cell; WBC, white blood cell.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

A differential count of 34% polymorphonuclear leukocytes (PMNs), 4% bands, 38% lymphocytes, and 24% monocytes; a hemoglobin level of 11.9 g/dL; and a platelet count of 262 \(\times 10^3/\mu L\). Results of serum chemistry studies were normal except for an elevated serum urea nitrogen level of 71 mg/dL (25.3 mmol/L) and creatinine level of 4.6 mg/dL (407 \(\mu\)mol/L), consistent with her chronic renal failure. She was treated with intravenous antibiotics, stress-dosed corticosteroids, and granulocyte colony-stimulating factor for empirical coverage of presumed bacterial infection in a setting of cyclophosphamide-induced leukopenia.

During the next 2 weeks the patient’s level of arousal fluctuated between coma and lethargy. Periods of intermittent tachypnea were observed. She had marked dysarthria and roving eye movements in the horizontal plane and could occasionally follow some commands with hand squeezing. There was marked increase in tone with cogwheel rigidity in upper extremities and hyperactive deep tendon reflexes; bilateral ankle clonus was noted but with equivocal Babinski signs. Follow-up CSF examination on the 17th hospital day yielded a protein level of 0.077 g/dL, glucose level of 78 mg/dL (4.3 mmol/L), RBC count of 0.000005 \(\times 10^6/\mu L\), and WBC count of 0.069 \(\times 10^6/\mu L\), but now a lymphocytic predominance was observed: 6% PMNs and 94% lymphocytes (Table). Serologic studies sent for antibodies to Rickettsia, parvovirus B19, and Brucella were negative; toxoplasmosis and Epstein-Barr virus antibody testing was positive for IgG but negative for IgM antibodies. Malaria organisms were not seen on blood smear, and multiple blood cultures yielded no growth. Polymerase chain reaction examination of CSF did not amplify DNA for herpesvirus 1 or 2, cytomegalovirus, *Mycobacterium tuberculosis*, or *Borrelia burgdorferi*. Cytologic examination of the CSF was negative. Thyroid function test results and complement levels were normal. Other imaging studies including single-photon emission computed tomography of the brain, cerebral MR angiography, and total-body indium scan were negative.

The patient was transferred to New York–Presbyterian Hospital, New York, NY, on the 22nd day after the initial hospitalization. She was afebrile and her neck was supple but she remained stuporous, responding only to painful stimuli. Brainstem reflexes were intact, with semipurposeful withdrawal of all 4 limbs and symmetrically brisk reflexes. A noncontrast computed tomographic scan of the head was normal, and an electroencephalogram (EEG) showed diffuse slowing but no epileptiform activity. Repeated CSF sampling yielded a protein level of 0.115 g/dL, glucose level of 68 mg/dL (3.8 mmol/L), RBC count of 0.000009 \(\times 10^9/\mu L\), and WBC count of 0.021 \(\times 10^9/\mu L\), with continued polymorphonuclear pleocytosis: 79% PMNs and 21% lymphocytes (Table). Cryptococcal antigen was not detected, and no organisms were seen on gram stain.

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Subtle linear hyperintense lesions on T2-weighted images in the posterior limb of the right internal capsule and superior lateral aspect of the right thalamus were also identified (images not shown). An MR angiogram of the circle of Willis and neck vessels was normal.

Three days later, the patient became tachypneic with bilateral hand jerking. An EEG showed moderate diffuse background slowing and frequent runs of frontally predominant rhythmic delta waves consistent with seizure activity. Phenytoin and valproic acid were begun. She subsequently became comatose with sluggish brainstem reflexes and required intubation and mechanical ventilation. Continuous EEG monitoring in the neurologic intensive care unit showed generalized background slowing and frequent spike-and-wave activity. She was treated for nonconvulsive seizures and given a continuous midazolam infusion.

Approximately 1 week later an electrocardiogram showed conduction abnormalities. Cardiac enzyme testing showed an elevated creatine kinase level of 906 IU/L, with a 13.6% MB fraction. Transthoracic echocardiogram showed mild global hypokinesis with regional wall motion abnormalities. These results were
interpreted as consistent with myocardial inflammation.

The viral cultures sent on CSF obtained at our institution yielded coxsackievirus B4 enterovirus. In addition, a rectal swab yielded coxsackievirus B4 enterovirus, suggesting actively shedding virus in our patient. A research laboratory (ViroPharma, Exton, Pa) was contacted and arrangements were made for compassionate use of pleconaril, an antipicornavirus agent.7 The patient received a 7-day course of pleconaril without overt side effects; however, she remained comatose. The patient’s hospital course was further complicated by pneumonia, anasarca, thrombocytopenia, deep venous thrombosis, and gastrointestinal tract bleeding. Fifty-three days after the onset of symptoms, she developed a fatal ventricular fibrillation.

A complete autopsy was performed that showed grossly normal brain, spinal cord, and meninges except for depigmentation of the substantia nigra bilaterally. Microscopic examination showed necrosis of the substantia nigra with near-complete loss of pigmented neurons and numerous macrophages, some containing a typical appearance of melanin (Figure, C and D). Basophilic spicules with a beaded appearance were scattered throughout the lesions, consistent with mineralized material. Similar but smaller lesions were located symmetrically in the lateral and superior aspects of the tegmentum. There were also sparse microglial nodules in the thalamus, inferior olivary nucleus, dentate nucleus, and cerebellar cortex. In particular, the dentate nucleus of the cerebellum was hypercellular with astrocytosis and neuronal loss. The macrophages and microglia were accompanied by a few scattered lymphocytes. No neurofibrillary tangles were specifically identified. The remainder of the brain and spinal cord were histologically normal. Examination of the heart showed extensive active myocarditis with moderate dilated cardiomyopathy. Additional pathological findings included vascular congestion and macrophages in the lungs, a bone marrow embolus in a small pulmonary artery, and near–end-stage chronic nephropathy.

This is the first reported case, to our knowledge, of documented coxsackievirus B4 infection presenting as encephalitis lethargica; however, we are cautious about overinterpreting this finding. It seems unlikely that coxsackievirus B4 is a causative agent of von Economo disease, since outbreaks of coxsackievirus B4 meningoencephalitis are not associated with encephalitis lethargica. We believe that the unusual pattern of illness in our patient was due to preexisting immunosuppression resulting in enhanced susceptibility to severe viral infection. Nevertheless, this case extends the pattern of illness attributable to coxsackievirus B4 infection.

The anteceding prodrome with signs of meningismus, fluctuating level of consciousness, increased tone, extrapyramidal signs, and respiratory disorder seen in our patient are reminiscent of encephalitis lethargica. Rare sporadic cases of encephalitis that bear striking similarity to von Economo disease have been reported since the time of the epidemic of 1915 to 1930.8,9 Because the causative agent of von Economo disease was never isolated, clinical diagnostic criteria were developed to identify sporadic cases of encephalitis lethargica.14,18 Indeed, the presence of impaired level of consciousness, central respiratory disturbance, and rigidity observed in our patient with encephalitis fit the proposed diagnostic criteria for encephalitis lethargica.14 However, our patient did not experience opthalmoplegia or oculargyric crises, nor was there observable sleep disorder and abnormal behaviors during the acute phase of illness that are characteristic of the von Economo somnolent-ophthalmoplegic type of encephalitis lethargica.14,16,19,20

A diagnosis of encephalitis lethargica is based on clinical presentation, cerebrospinal findings, EEG, and pathological features. von Economo19 described 3 clinical forms of the disease: the most common, the somnolent-ophthalmoplegic form, begins with an influenzalike illness followed by drowsiness and confusion progressing to coma associated with external ophthalmoplegia, oculargyric crises, and nystagmus as early features; the other 2 forms are Bradykinesia-catalepsy-mutism and hyperkinesia, the latter of which is associated with extreme motor restlessness, visual hallucinations, and dyskinesias. Clinical features considered major criteria supporting the diagnosis of encephalitis lethargica include an acute or subacute encephalitis associated with at least 3 of the following major criteria: signs of basal ganglia involvement, oculargyric crises, ophthalmoplegia, obsessive-compulsive behavior, akinetic mutism, central respiratory irregularities, or somnolence and/or sleep inversion.20 The CSF is frequently abnormal, with signs of meningeal irritation, ie, increased pressure and protein content and mild or moderate predominantly lymphocytic pleocytosis that can be seen in the early stages. The CSF glucose level is invariably normal, but oligoclonal band positivity has been reported.21 An EEG during the acute phase of the illness often shows diffuse unilateral or bilateral slowing in the delta or theta frequencies and focal sharp-wave activity.14 Pathological findings of von Economo disease typically consist of a nonhemorrhagic involvement of the gray matter, preferentially in the midbrain. Although the most severe involvement is usually isolated to the brainstem and basal ganglia, cerebral cortex and spinal cord can be affected as well.14,22 The pathological hallmark of the disease is cytoplasmic inclusions of neurofibrillary tangles within the substantia nigra, often associated with severe neuronal loss.22

The MR imaging studies in our patient showed unusual hyperintense signals on both T1- and T2-weighted imaging in the substantia nigra bilaterally (Figure, A and B). The basis for these signal changes is uncertain. However, pathological changes seen at autopsy correlate anatomically with the MR imaging findings. Thus, the T1- and T2- hyperintense signals on MR imaging seen in our patient may be due to tissue necrosis and mineralization of the lesions. Microhemorrhages could give rise to hyperintense T1- and T2-weighted signals, although there was no histological evidence to support this suggestion at autopsy. Identical MR imaging findings were recently reported in a case of encephalitis lethargica.21 In that report, both T1- and T2-weighted hyperintensity was also seen in the substantia nigra, and...
the patient survived the acute encephalitis but developed postencephalitic parkinsonism. No causative agent was identified.

The substantia nigra was selectively involved in our patient and is reminiscent of the pathological changes seen in cases of postinfectious parkinsonism and encephalitis lethargica.23,25 Although pathological involvement of the basal ganglia and thalamus frequently occurs in postencephalitic parkinsonism and encephalitis lethargica, these structures appear less frequently and severely affected than the preferential involvement of the substantia nigra. Indeed, pathological findings in our case are strikingly similar to those in 4 patients with postencephalitis parkinsonism reported by Bojinov,23 one of whom had died of concurrent myocarditis. In this patient a virus was isolated but not identified. It is possible that coxsackievirus B4 may be another causative agent of this syndrome, since, as in our case, viral infection of the central nervous system was associated with destruction of the substantia nigra. However, it is speculative to say whether our patient would have had delayed onset of parkinsonism had she survived.

While the coxsackievirus B4 might be implicated in the evolution of parkinsonian symptoms, it is less clear how it caused profound coma in our patient. The diffuse slowing seen on EEG and seizure activity suggest that cerebral cortex was affected by the meningoencephalitis. Similar observations were described in cases of postencephalitic parkinsonism.14,23 It is curious that there was no extensive injury to the reticular activating system or cerebral cortex that could account for the coma. The diffuse subcortical white-matter astrogliosis in a case of von Economo encephalitis lethargica and in another case of postencephalitic parkinsonism described by Elizan and Casals25 was not seen in our case. Perhaps these structures were involved earlier in the course of the infection and were no longer compromised at the time of the patient’s death, or the viral infection produced diffuse cerebral dysfunction by mechanisms other than tissue destruction.

Although the causative agent of von Economo encephalitis was never identified,26 a viral agent is implicated by pathological study.25 Subsequently, several viruses have been causally linked to postencephalitic parkinsonism. The coxsackievirus B2 was implicated in 2 cases of postencephalitic parkinsonism.27,28 A few patients infected with Japanese encephalitis virus showed signs of parkinsonism, either early in the course of the illness or as a long-term sequela.29,30 Postencephalitic parkinsonism was also reported after an outbreak of western equine virus31 as well as measles32 and Mycoplasma33 infections. Why infections by these agents would cause parkinsonism is not clearly understood, but it is assumed that injury to the substantia nigra is likely the common mechanism.

It is unclear why our patient developed severe encephalitis from a virus that causes mild aseptic meningitis in adults.2,6,34 Nevertheless, fatal coxsackievirus infections are observed in infants and children2,25-31 and in patients with agammaglobulinemia.36-40 Enteroviral infection can be life-threatening in the setting of immunosuppression. We observed that our patient became infected by coxsackievirus while undergoing immunosuppressive treatment for Henoch-Schonlein purpura and IgA nephropathy. Therefore, it is likely that immune suppression or possibly abnormalities intrinsic to her immune system made the patient susceptible to a more fulminant course of infection. There are similarities in the pathological changes in our patient to those seen in infantile coxsackievirus encephalitis41,42 and the enteroviral chronic meningoencephalitis of agammaglobulinemia43,44; however, in our patient there was less lymphocytic infiltration. Furthermore, severe changes in the substantia nigra seen in our patient are not seen in infantile coxsackievirus encephalitis or the enteroviral chronic meningoencephalitis of agammaglobulinemia, which spare this nucleus. There are no reports of postencephalitic parkinsonism in infantile enteroviral meningoencephalitis or in agammaglobulinemia.

Newer treatments such as pleconaril7,8 may provide benefit in the treatment of life-threatening enteroviral infections.45 However, early identification of the causative agent is vital for potential effectiveness of these therapies. Repeated viral cultures of the oral mucosa, rectal mucosa, and CSF are recommended in all patients suspected of having meningoencephalitis, and serologic testing now available for most enteroviruses. This latter method may be a more practical assay for detection of infection, since standard viral cultures require rapid delivery to a virology laboratory for incubation. Polymerase chain reaction–based assays on CSF may eventually replace these other methods of enteroviral detection.46

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REFERENCES