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Critical Report

Persistent Coxsackie B encephalitis: Report of a case and review of the literature

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Although the diagnosis is rarely confirmed, enteroviruses are a common cause of meningitis. Coxsackie B is responsible for more than half of the cases of aseptic meningitis in infants less than 3 months old, but is less common as a cause of neurological disease in older persons. In addition to aseptic meningitis, Coxsackie B has been reported to cause a wide range of other neurological disorders, albeit rarely. The authors report a young adult with persistent Coxsackie B encephalitis that was heralded by focal seizures and evolved to intractable coma with multifocal myoclonus. The diagnosis was established by immunohistochemistry and reverse transcriptase–polymerase chain reaction (RT-PCR) on tissue obtained at brain biopsy. Cerebrospinal fluid (CSF) viral cultures and PCR were negative for enteroviruses. This case highlights unusual features of a persistent infection that could easily have been mistaken for a neurodegenerative or other noninfectious process. It also emphasizes the importance of performing brain biopsy on individuals with neurological disease of obscure nature. *Journal of NeuroVirology* (2006) **12,** 511–516.

Introduction

We report a patient with persistent Coxsackie B encephalitis who initially presented with an afebrile illness characterized by focal seizures. Over the course of several weeks, she developed intractable coma with multifocal myoclonus. Diagnosis of this infection required a brain biopsy and the application of a battery of studies on the brain tissue not routinely employed, namely, immunohistochemistry and polymerase chain reaction (PCR) for enteroviruses.

The enteroviruses are ubiquitous and account for the majority of viral illnesses worldwide (Ropka and Jubelt, 2003). Neurological disease is a well recognized complication of enterovirus infection. Cerebrospinal fluid (CSF) analysis by PCR indicates that approximately two thirds of aseptic meningitis are the consequence of enterovirus (Rotbart, 1990; Sawyer *et al*, 1994). Enteroviruses have been estimated to be responsible for 75,000 cases of meningitis in the U.S. annually (Rotbart, 1997). Although less common in older individuals, Coxsackie B virus is responsible for 62% of the cases of aseptic meningitis in infants less than 3 months of age (Kaplan *et al*, 1983). In addition to aseptic meningitis, Coxsackie B has been associated with encephalitis (Jarcho *et al*, 1963; 1968; Erickson *et al*, 2003; Brunner *et al*, 2004), postencephalitic parkinsonism (Poser *et al*, 1969; Albert *et al*, 1974; Peatfield, 1987), acute disseminated encephalomyelitis (ADEM) (David *et al*, 1993), Reye's syndrome (Kaul *et al*, 1979), Bell's palsy (Mertens *et al*, 1982), disorders of the hypothalamic-pituitary axis (Hagg *et al*, 1978), and flaccid paralysis (Saraswathy *et al*, 2004; Kelly *et al*, 2006). In neonates, severe neurological sequelae may follow Coxsackie B (Farmer et al, 1975), perhaps more so than with other enterovirus infections (Wilfert *et al*, 1981).

Results

A 19-year-old, right-handed, white female nursing student with an unremarkable prior medical history

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developed recurrent spells of numbness of her right face and tongue and slurred speech on January 28th, 2005, 2 weeks after a nonspecific upper respiratory illness. The episodes were paroxysmal and lasted up to 1 h. Subsequently, an involuntary contracture of the fingers of the right hand would accompany the spells of numbness. She was then noticed to frequently become lost in familiar environments and uncharacteristically performed poorly on her classes. Transient phenomena followed including peculiar perceptions, such as, that "the sky appeared bigger than it should" and visual hallucinations of "box-like structures with squiggly lines" in the right visual field. A detailed neurological examination performed approximately 2 weeks after the start of her symptoms was unremarkable.

On February 22nd, she was found by her mother on the bathroom floor, confused and nauseous. The first-ever witnessed tonic seizure ensued and she was admitted to hospital. She denied headache, neck stiffness, malaise, fever, or chills. On February 24th, she developed auditory hallucinations characterized by the repetition of familiar movie themes and expressed the desire "to make movies." She exhibited echolalia and excessive fear, including the fear of sleeping. In between these spells, she was able to converse normally, engage in activities such as playing cards, and fully cared for herself.

Focal motor seizures involving the right side more often than left and rare generalized seizures were observed. Her initial electroencephalogram (EEG) revealed status epilepticus. Control of the seizures required the use of propofol and midazolam; however, following the weaning of these medications, she remained comatose. She had also been treated with acyclovir for possible herpes encephalitis. Repeat EEG on February 27th showed generalized slowing greater over the left hemisphere and subsequent EEGs revealed left-sided sharp waves and spikes without a recurrence of her status epilepticus.

A computed tomography (CT) scan of her head with and without contrast was normal. Cranial magnetic resonance imaging (MRI) obtained on February 27th showed an abnormal signal in both medial temporal lobes, best seen on FLAIR and T2-weighted images (Figure 1). No contrast enhancement was observed. A subsequent cranial MRI obtained on March 2nd showed some improvement in this finding and by March 8th, these abnormalities had largely resolved; however, a new hyperintense signal was seen in the left putamen (Figure 2). No edema, mass effect, or contrast enhancement was noted. An magnetic resonace angiogram (MRA) and standard cerebral angiogram were normal.

The initial cerebrospinal fluid analysis from February 23rd showed 10 red blood cells (RBCs)/mm^3, 110 white blood cells (WBCs)/mm^3 (10 monocytes, 82 lymphocytes, 10 polymorphonuclear cells), protein 39 mg/dl, glucose 69 mg/dl, negative venereal disease research laboratory (VDRL) test–negative herpes simplex virus (HSV) PCR, and negative routine microbiologic studies. A repeat CSF analysis on March 3rd showed 9 RBCs/mm^3, 20 WBCs/mm^3 (7 monocytes and 91 lymphocytes), protein 30 mg/dl, glucose 72 mg/dl. CSF PCR for HSV, Epstein-Barr

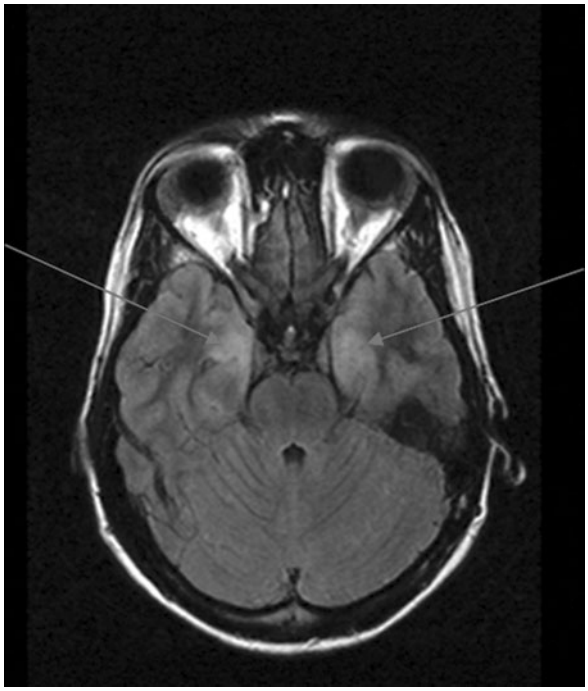

Figure 1 MRI from February 27th, 2006. Hyperintense signal abnormalities are seen on FLAIR in the medial aspects of both temporal lobes *(arrows)*.

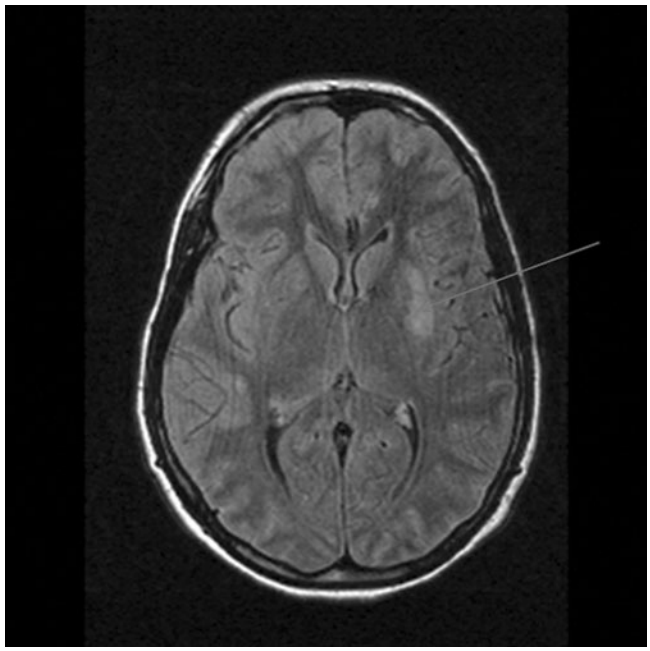

Figure 2 MRI from March 8th, 2006. A hyperintense signal is observed in the left putamen on FLAIR image *(arrow)*. The lesions in the temporal lobes had largely resolved at the time of this study.

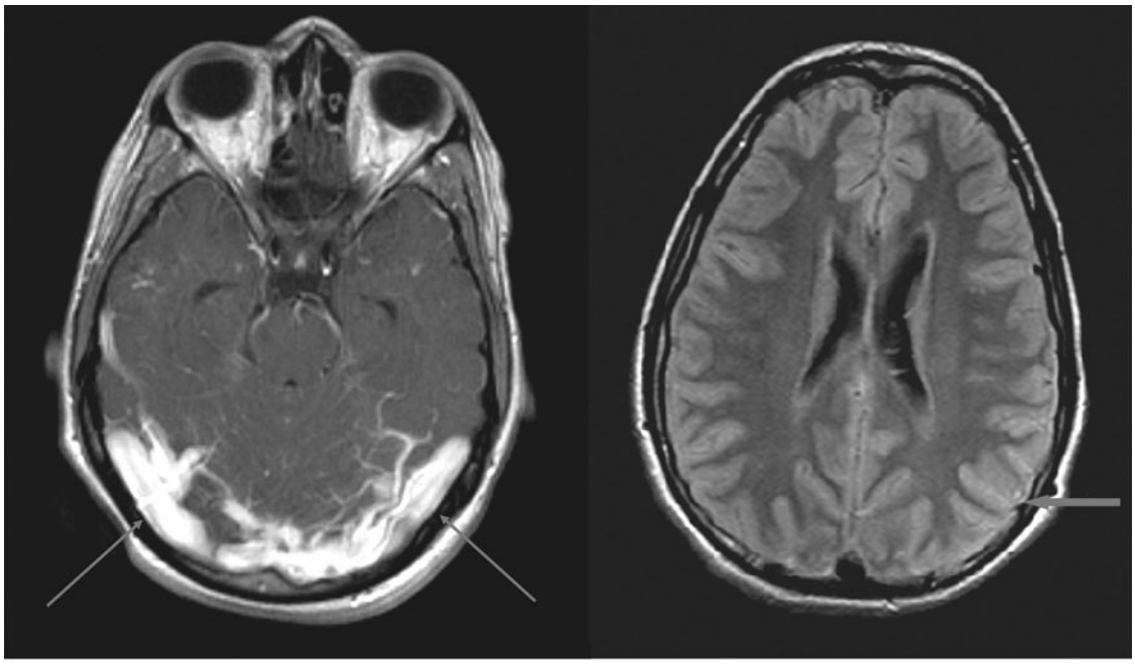

Figure 3 MRI from March 23rd, 2006, T1 postcontrast axial image (**A**) reveals marked distention and congestion of the transverse sinuses and cortical veins along tentorium *(arrows).* Similar findings were evident within the cortical venous structures at the convexities. Axial fluid attenuated inversion recovery (FLAIR) image (**B**) reveals subtle areas of hyperintensity within the left parietal cortex *(arrow).*

virus, mycoplasma, enterovirus, and *Mycobacterium tuberculosis* were negative. CSF cryptococcal antigen was negative. Cultures for bacteria, including mycobacteria, viruses, and fungi were negative. Serological studies for cytomegalovirus and blastomycosis were negative. Studies for pertussis were negative. Urine histoplasmin test was negative. Lyme antibody was negative. Epstein-Barr virus early immunoglobulin G (IgG) was negative, but viral capsid antigen (VCA) IgG and Epstein-Barr nuclear antigen (EBNA) were elevated at 75 and 96, respectively, indicative of a remote EBV infection. Human immunodeficiency virus (HIV) serology was negative. Rabies antibody studies were negative. Serological studies for toxoplasma and lymphocytic choriomeningitis were also negative.

Her WBC was 9400 with normal differential. Her sedimentation rate was 33 mm/h and C-reactive protein 2.4. Routine chemistries including liver function and thyroid studies were normal. A battery of rheumatological studies was negative including antinuclear antibody and antineutrophil cytoplasmic antibody. The angiotensin-converting level was normal at 14. A panel of paraneoplastic antibodies (Athena Diagnostics, Worcester, MA) was negative.

Repeat CSF analysis on March 3rd revealed 20 WBCs/mm^3 (91% lymphocytes, 9% monocytes), glucose 72 mg/dl, and protein 30 mg/dl. All microbiological studies including repeat PCR for HSV and EBV were negative. CSF angiotensin-converting enzyme was normal.

Physical examination on March 12th revealed an afebrile, well-developed, comatose young woman, ventilator dependent with a respiratory rate of 12/min. Vital signs were otherwise normal. Her general physical examination was normal. Pupils were 4 mm and briskly reactive to light. The funduscopic examination was normal. Corneal reflexes were depressed. Oculocephalic testing was normal. The face was symmetric. Extremity tone was diminished and there was no response to noxious stimuli. Reflexes were 1+ in the upper extremities and knees and 2+ at the ankles. Plantar responses were flexor.

On March 22nd, CSF analysis showed 3 WBCs/mm^3 (100% lymphocutes), glucose 59 mg/dl, and protein 22 mg/dl. Bacterial, fungal and viral cultures were negative. A repeat MRI from March 23rd showed mild signal changes, best seen on FLAIR in the left posterior and superior cerebral hemispheres, particularly evident in the left parietal convexity (Figure 3). Engorgement of the venous structures was also observed. A brain biopsy obtained from the right frontal lobe was performed on March 31st showed increased eosinophilia of the neuronal nuclei, but the cytoplasm was undisturbed and there were no features to suggest inflammation of either the cerebral cortex or subcortical white matter. Immunohistochemistry for enteroviral protein was positive using a method previously described (Cioc and Nuovo, 2002); unremarkable brain from a person who died of a myocardial infarct and Coxsackie myocarditis served as the negative and positive controls,

respectively. As seen in Figure 4, viral protein localized eccentrically to the cytoplasm. Immunohistochemical staining of a control brain was negative (Figure 3B). Reverse transcriptase (RT)–in situ PCR for primers that detect the Coxsackie B serotypes as previously described (Cioc and Nuovo, 2002) was positive with viral RNA, like the protein, noted in an eccentric cytoplasmic pattern often bordering on the nuclear membrane (Figure 4A). RT–in situ PCR was negative for measles, rabies, rotavirus, and parvovirus and the same controls noted above gave the expected results.

During the course of hospitalization, her mental status fluctuated between an agitated stuporous state and coma. Continuous multifocal myoclonus developed, which was attenuated during sleep and sedation. There were no electroencephalographic correlates for the myoclonus. She also developed transient hyperpyrexia, tachycardia, diaphoresis, and tremors that responded to a combination of lorazepam, Benadryl, morphine sulfate, and haloperidol. Her clinical status remained unchanged through the termination of her acute hospitalization on April 21st, 2006, when she was transferred to a rehabilitation facility. With the exception of the early administration of acyclovir for suspected herpes simplex encephalitis, no specific antiviral therapy or immunotherapy (corticosteroids, plasmapheresis, or intravenous IgG) was initiated. Modest clinical improvement evidenced by occasional meaningful language was noted by September 2006.

Discussion

Coxsackie viruses were named in 1947 after Coxsackie, NY, when the virus was transmitted to suckling mice from children with a poliomyelitis-like illness (Dalldorf and Sickles, 1948). Like other enteroviruses, it is a small RNA virus that replicates at 37°C., lacks a lipid envelope, and is stable at acid pH (Ropka and Jubelt, 2003). As in our patient, it may cause a nonspecific upper respiratory (Melnick, 1985). Coryza, laryngotracheobronchitis, bronchiolitis, pleurodynia, and pneumonia have all be reported with Coxsackie B (Eckert *et al*, 1967; Dery *et al*, 1974; Chong *et al*, 1975; Melnick, 1985). Following replication in lymphatic tissues, a primary viremia ensues, but does not usually result in central nervous system (CNS) invasion. The latter generally occurs after amplification of viral titers in non-neural tissues (Ropka and Jubelt, 2003).

Most enteroviral infections are asymptomatic. Infection of the CNS may occur by hematogenous dissemination or by axonal transport, particularly, when nerve terminals or muscles are damaged (Greenberg *et al*, 1952; Ren and Racaniello, 1992). Damage to the CNS tissues may result from viral replication or indirectly as a consequence of an autoimmune mechanism (Muir and van Loon, 1997). The precise

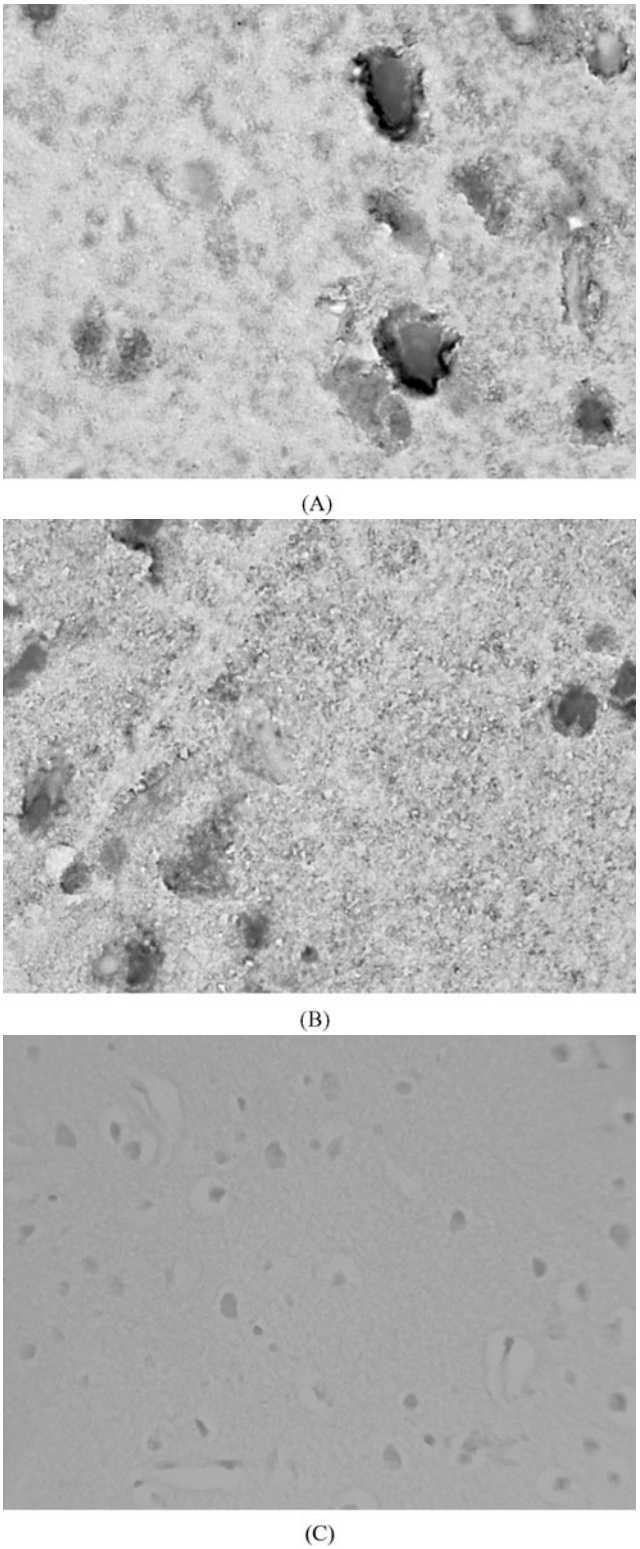

Figure 4 (**A**) Immunohistochemical stain for enteroviral protein in the patient showing its localization eccentrically in the cytoplasm (lighter internal region—RNA; darker outer rim—protein). (**B**) Immunohistochemical stain for enteroviral protein in a control brain showing absence of staining for the protein. (**C**) Immunohistochemical stain for Coxsackie RNA—negative control. Low-power magnification from the same area of the brain as **A** and **B** showing absence of staining for RNA.

mechanisms leading to cell death remain obscure. Among the proposed mechanisms are viral inhibition of cellular macromolecular synthesis, toxicity of various viral polypeptides, and virus-induced apoptosis (Muir and van Loon, 1997). To date, there is no specific treatment of enteroviral infections (Muir and van Loon 1997).

There are a number of very interesting features of this case. Firstly, the infection was only demonstrated as a consequence of brain biopsy. The routine histopathological features were bland and without a characteristic inflammatory response suggesting encephalitis. Only immunohistochemical studies and PCR enabled the diagnosis. Secondly, persistent infection occurred in the absence of any history or laboratory features to suggest an immunodeficiency. Unfortunately, detailed immunological studies were not performed as she was transferred elsewhere by the time the diagnosis was established. Although persistent infection with enterovirus is typically the consequence of a B-cell abnormality, it may be observed with both cellular and humoral immunodeficiencies (Melnick 1985). The most common enteroviral persistent infection is with ECHO virus in children with agammaglobulinemia (McKinney *et al*, 1987). Persistent infection may last for months or years (Girard *et al*, 2002) and the CSF may yield virus for up to 3 years (Hodes and Espinoza 1981). Persistent enteroviral infection of the CNS may be seen in the absence of positive CSF viral cultures (Rotbart *et al*, 1990). As is likely to have been the case in our patient, persistent Coxsackie B infection has been reported in immunocompetent individuals (Barnass, 1986). Thirdly, the only CSF abnormality was a moderate lymphocytic pleocytosis that cleared despite worsening symptoms and persistent viral infection. Neither viral culture nor enteroviral PCR on the CSF revealed the diagnosis. Normal CSF has been reported in patients with severe encephalitis due to enterovirus (Hart and Miller, 1973).

From time to time, physicians encounter patients with unusual neurological disorders of uncertain etiology. Despite exhaustive diagnostic evaluations, their medical illnesses often remain a conundrum. The demonstration of a persistent Coxsackie B virus in the face of rather bland histological findings raises the possibility that persistent viral infection may also contribute to the illness of other patients presenting similarly or even in patients with otherwise unexplained neurodegenerative processes. Had the studies simply consisted of routine histopathology rather than the application of immunohistochemistry and PCR to demonstrate the presence of Coxsackie B, the diagnosis would have remained obscure. This patient's course argues for a broader application of brain biopsy as a diagnostic study with the routine performance of studies for persistent viral infection.

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