J. Neurovirol. (2016) 22:538–540
DOI 10.1007/s13365-015-0418-z

CASE REPORT

Enterovirus causes rapidly progressive dementia in a 28-year-old immunosuppressed woman

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Received: 6 August 2015 / Revised: 15 December 2015 / Accepted: 16 December 2015 / Published online: 4 January 2016

Abstract Enterovirus in the nervous system can present with protean manifestations, including polio-like paralysis, movement disorders, and seizures. This is a report of a single case of a rapidly progressive dementing illness in a young woman with common variable immunodeficiency (CVID). Over the course of several months, she developed profound aphasia, apraxia, and cerebellar signs. She underwent brain biopsy which was suggestive of toxoplasmosis; despite an adequate course of treatment, she continued to decline and ultimately died. Autopsy and PCR testing revealed diffuse coxsackie B3 infiltration in the meninges and brain parenchyma. To our knowledge, this is the first description of enterovirus causing a dementing illness in a young immunosuppressed adult. We highlight the need for a broad differential diagnosis, especially for immunocompromised individuals, who may present in an atypical fashion.

Keywords Enterovirus · Coxsackievirus · Cognitive impairment · Common variable immunodeficiency

Introduction

Coxsackie B virus is a common cause of aseptic meningitis in children. Adults less frequently develop active disease, due to immunity acquired in childhood. However, in the immunosuppressed host, the virus may reactivate due to loss of antibody-mediated defense mechanisms (Berger et al. 2009; Peatfield 1987). In adults, the disease can have many more atypical presentations and increased morbidity compared to childhood infection. Here, we present a case of a woman with CVID with rapidly progressive dementia caused by coxsackie B infection.

Case

In early autumn, a 28-year-old woman presented to our tertiary care center with a 6-month history of progressive confusion and memory loss. Several months prior to the onset of symptoms, she had been diagnosed with common variable immunodeficiency (CVID). Treatment consisted of infusions of intravenous immunoglobulin, dosed at 400 mg/kg every 4 weeks. After two treatments, she noted low-grade fevers following each infusion, thought to be a mild Jarisch-Herxheimer reaction. The regimen was adjusted to 500 mg/kg every 21 days. She had received a total of eight infusions before presentation.

Her family noted that she was having difficulty completing a sentence, recalling the names and telephone numbers of close friends, and reading to her young daughter. Her general medical examination was notable for a fine macular truncal rash. On neurologic examination, she had impaired delayed word recall, staccato-like spontaneous speech with preserved repetition, inability to read even simple sentences, and complex anomia. There was also bilateral paratonia, apparently intact power, and right-sided hyperreflexia, dysmetria, and dysdiadochokinesia.

She was admitted to the general neurology service and underwent magnetic resonance imaging (MRI) of the brain with and without contrast, followed by a lumbar puncture. MRI revealed multiple symmetrical areas of high T2/FLAIR

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signal involving the subcortical white matter and cortex bilaterally at the frontal vertex, bilateral insula, and anterior and mesial temporal lobes, with additional patchy signal abnormality in the pons and the cerebellum (Fig. 1), suggestive of a nonspecific inflammatory process. There was no abnormal leptomeningeal or parenchymal enhancement. Lumbar puncture showed an opening pressure of 23.5 cm H2O, cell count of 7 WBC and 4 RBC, glucose of 53, and protein of 44. Flow cytometry of the CSF demonstrated a paucity of B cells, as expected in CVID. Other negative CSF studies included cryptococcal antigen, HSV PCR, varicella PCR, enterovirus PCR, JC virus PCR, Lyme PCR, and syphilis antibody. A serum paraneoplastic panel was negative.

Clinically, she continued to decline with frequent falls. Brain biopsy was performed, with samples taken of the left cortex, subcortical white matter, uncus, and insula. Immunohistochemical stain for *Toxoplasma gondii* was positive at all four sites, though no tachyzoites were seen. Additional stains for HSV, CMV, JCV, tuberculosis, and silver stain were all negative. In the serum, toxoplasma IgG was positive; IgM was equivocal. She was discharged from the hospital with the diagnosis of atypical cerebral toxoplasmosis and a 6-week course of pyrimethamine and sulfadiazine.

Despite this treatment, her clinical course continued to decline and she was re-admitted 2 months later. Her examination on readmission was notable for mutism, diffuse tremulousness, choreiform movements of the neck, and intermittent myoclonic jerks of the arms. Repeat lumbar puncture showed an opening pressure of 7 cm H2O, cell count of 6 WBC and 5 RBC, protein of 44, and glucose of 52. Bacterial, viral, and fungal testing was negative. With continued diagnostic uncertainty in the face of rapid neurologic decline, she underwent repeat brain biopsy, which showed a nonspecific meningoencephalitis. Toxoplasma immunostain was seen intravascularly, indicating a false positive result. Her post-operative course was complicated by a left middle cerebral artery infarction, after which her family requested comfort measures. She passed away shortly thereafter and came to autopsy.

On autopsy, fresh brain weight was 1160 g. Gross examination of the brain was unremarkable. Microscopy confirmed diffuse meningoencephalitis in the cerebral cortical hemispheres, deep gray nuclei, cerebellum, and brainstem. Specimens from the uncus and parietal lobes were sent to the National Institutes of Health for analysis, which revealed human coxsackievirus B3 by tissue PCR.

Discussion

Coxsackie B is a non-polio enterovirus which typically causes a nonspecific febrile illness in the summer and fall months. The virus is transmitted by the fecal-oral route and enters the bloodstream via the small intestine. Enteroviridae are neurotropic, entering neural progenitor stem cells in vitro via multiple target receptors (Feuer et al. 2005). Coxsackievirus, in particular, appears to be specific for the choroid plexus, hippocampus, and cortex (Feuer et al. 2005). Murine infection disrupts spatial memory pathways and causes hippocampal atrophy (Buenz et al. 2006), but this has not been formally tested in the human population.

In the CNS, coxsackievirus produces a range of clinical phenotypes. It accounts for up to 50 % of cases of aseptic meningitis in children under the age of 3 months (Bottner et al. 2002). Adult infection is less common in adults but not rare; between 1983 and 2005, adults over 20 years of age accounted for 17.3 % of known coxsackie diagnoses (Enterovirus Surveillance 2005). In the adult population, coxsackie B meningoencephalitis has been associated with seizures (Berger et al. 2006), parkinsonism (Jang et al. 2009) and, in one case report,

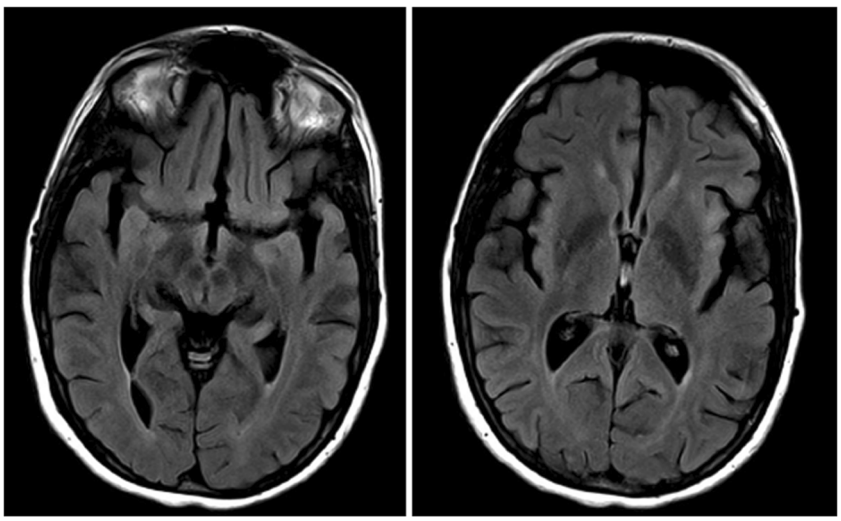

Fig. 1 MRI demonstrating confluent FLAIR hyperintensities in the insula, bilateral mesial temporal lobes, and subcortical white matter

with a relapsing-remitting multiple sclerosis-like illness in a patient with AIDS (Berger et al. 2009). Coxsackie B virus has also been proposed as a possible causative agent in encephalitis lethargica (Cree et al. 2003) and schizophrenia (Rantakallio et al. 1997). One prior case report implicates coxsackie B as the cause of rapidly progressive dementia (Valcour et al. 2008), although that patient, unlike ours, was elderly and was immunocompetent.

To our knowledge, this is the first case report of coxsackie B virus causing meningoencephalitis and rapidly progressive dementia in an adult patient with CVID. Presumably, her inability to generate an antibody response led to reactivation of a latent childhood infection. Immunodeficiency syndromes present a unique diagnostic challenge in the neurologic patient, as standard antibody-dependent serologic markers are frequently negative, yet these patients are at increased risk of reactivation as well as primary infection. This case highlights the importance of casting a wide net when considering diagnoses in immunocompromised adult patients.

Authors' contributions SM performed literature review and drafted the manuscript. BBS drafted the manuscript and provided supervision.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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