FATAL WILD-TYPE VARICELLA-ZOSTER VIRUS ENCEPHALITIS WITHOUT A RASH IN A VACCINATED CHILD

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Abstract: Encephalitis associated with varicella-zoster virus, rare among children in the varicella vaccine era, has generally been associated with a rash. We report fatal wild-type varicella-zoster virus encephalitis without a rash in a child who had received 1 dose of varicella vaccine. Varicella-zoster virus encephalitis should be considered in the differential diagnosis for children presenting with acute neurologic symptoms, even vaccine recipients.

Key Words: encephalitis, varicella aoster, fatal outcome, chickenpox vaccine, zoster sine herpete

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Varicella-zoster virus (VZV) causes varicella as primary infection; virus remains latent and can reactivate to cause herpes zoster. Neurologic complications associated with both illnesses, albeit rare, have been reported among both healthy and immunocompromised patients.[1]

In the United States, varicella vaccination has substantially reduced the incidence of varicella and the rates of hospitalization and death. Nevertheless, approximately 15%–20% of persons vaccinated with 1 dose of varicella vaccine can develop disease (ie, breakthrough varicella) if exposed to varicella. Breakthrough cases usually are mild, with few lesions, and some can go unrecognized.[2]

We report a fatal VZV encephalitis illness without a rash in a child who had received 1 dose of varicella vaccine. VZV encephalitis should be considered in the differential diagnosis for children presenting with acute otherwise unexplained neurologic symptoms, even vaccine recipients, to guide appropriate treatment.

CASE REPORT

In June 2011, a pediatrician notified the New Mexico Department of Health that a 4-year-old female patient died of VZV encephalitis. A varicella death investigation was conducted, because varicella is a notifiable disease in New Mexico.

The patient was admitted to the hospital in February 2011, after complaining of sudden severe headache and right eye pain. During the 10 days before admission, she had experienced frequent and intermittent episodes of vomiting, headaches, seizures, lethargy, low-grade fever, mental status changes, poor interaction and poor appetite. She did not have cough, abdominal pain, diarrhea or rash. No history of recent travel or known sick contacts at home or the child care center she attended were noted. She had received 1 dose of varicella vaccine at 13 months of age and had no history of varicella disease. Her medical history was remarkable for nasal septum perforation with subsequent recurrent sinusitis requiring prolonged courses of antibiotic therapy. Additionally, she had hypocalcemia-related seizures at 1 year of age secondary to partial hypoparathyroidism; a DiGeorge syndrome workup including a fluorescence in situ hybridization test for 22q11 chromosomal deletion was negative. No documentation of T- and B-cell subsets being performed was found. She received calcium supplements and had no more seizures. The patient had no history of chronic medical conditions or immunosuppressive medications, was born full term without reported complications, had reached appropriate developmental milestones and had performed adequately at preschool.

On physical examination, the patient was drowsy, drooling, lethargic and increasingly unresponsive to verbal stimuli. Her vital signs were normal. Neck was supple. Pupillary reflexes and fundoscopy were normal. She had a right gaze preference and probable left hemianopia with some tremors in her extremities. No rash or dysmorphic features were noted. Her general and neurologic examinations were otherwise unremarkable.

Laboratory data revealed a white blood cell count of 10×10^9/L (neutrophils 85%, lymphocytes 7%, monocytes 8%); platelet count was 287×10^9/L. Total calcium was 8.6 mg/dL (normal, 8.5–10.1) and ionized calcium was 1.07 mmol/L (normal, 1.15–1.27). The patient's electrolyte panel, glucose, liver enzymes and renal function tests were within normal limits. Blood cultures were negative. Lumbar puncture and cerebrospinal fluid tests were not performed. No extensive laboratory evaluation of immunocompetence was performed.

A computed tomography (CT) brain scan showed a discrete enhancing lesion measuring 3×3 cm without ring enhancement in the right posterior parietal lobe with surrounding vasogenic edema, indicating an infectious or inflammatory process. A well-defined abscess was not clearly identified, and an underlying mass lesion could not be excluded. Follow-up magnetic resonance imaging was consistent with a primary glial neoplasm with local mass effect (Fig. 1A). A head CT scan in 2008 after her hypocalcemic seizure indicated no brain abnormalities. A facial CT scan in February 2011, approximately 2 weeks before her hospital admission, demonstrated a perforated nasal septum, paranasal sinus opacification and an enhancing mass suggestive of redundant nasal mucosa, enlarged vomeronasal organ or nasal glioma. Recommended nasal endoscopy and biopsy were not performed.

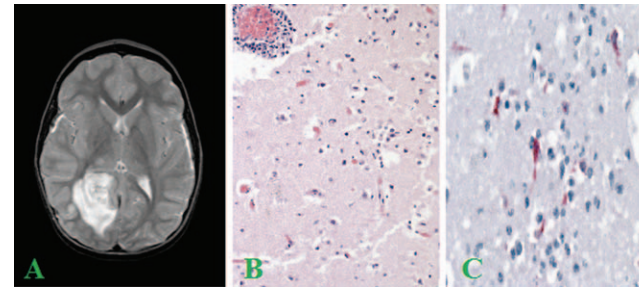

FIGURE 1. A, T2 wighted magnetic resonance image of the brain. B, Brain tissue showing neuronal necrosis and perivascular lymphosytic inflmmation (Hematoxylin and Eosin statin). C, Immunohistochemical stain revealing VZV antigens (red) within multiple neurons.

The patient was given a preliminary diagnosis of primary brain tumor, with mild local mass effect, and treated with supportive measures. No antibiotics or antivirals were administered. The patient's condition worsened, and during hospital day 4 she developed symptoms of increased intracranial pressure. An electroencephalogram revealed strong epileptiform activity in the area of the suspected tumor and subclinical seizures on video electroencephalogram monitoring. A head CT scan indicated no changes. During hospital day 5, the patient's symptoms worsened, and she had no pupillary light reflex. An emergent head CT scan indicated an obstruction of the fourth ventricle and evidence of herniation. She underwent emergent external ventricular device placement. Intraventricular pressure monitoring beginning at that time revealed extremely elevated pressures. On hospital day 6, the day the patient died, a cerebral perfusion study indicated no intracerebral blood flow, consistent with brain death.

A postmortem examination was performed. The brain appeared swollen with tissue softening and hemorrhages. No discrete brain lesion was grossly visible. A biopsy of the right side of the brain was performed. Microscopic examination revealed necrosis with inflammation, including clusters of microglia, consistent with encephalitis. No evidence of a tumor was observed.

Brain specimens were sent to the Centers for Disease Control and Prevention for additional testing. Multifocal encephalitis with viral-like inclusions was seen by hematoxylin-eosin stain (Fig. 1B). Extensive multifocal immunohistochemical staining of VZV antigens was seen in association with tissue damage; no evidence of herpes simplex virus or bacterial infection was observed (Fig. 1C). Polymerase chain reaction testing of DNA extracted from specimens was positive for wild-type VZV.[3] VZV encephalitis was determined to be the cause of death.

DISCUSSION

To our knowledge, this is the first reported fatal case of VZV encephalitis in a child who had received 1 dose of varicella vaccine. Additionally, the child did not have rash. Two major pathologic mechanisms have been proposed as contributing to the development of VZV encephalitis: direct viral invasion of the brain and an autoimmune process.[4] The findings in this case, including acute presentation, localization of viral antigens in encephalitic lesions and detection of VZV DNA from brain tissue, suggest direct viral invasion.

Among children who have received varicella vaccine, nonfatal neurologic complications have been reported rarely after varicella or herpes zoster; a few of these were confirmed to be a result of vaccine-strain VZV.[5,6] Among unvaccinated persons, wild-type VZV is known to cause fatal neurologic complications.[7] Because the patient described in this report had received 1 dose of varicella vaccine and had no recognized evidence of an immunocompromising condition, her clinical presentation raises questions about why the illness was fatal, and we found no conclusive answers.

Although VZV-associated illness generally manifests with rash, encephalitis related to primary VZV infection without a rash in an unvaccinated immunocompetent child was described in 1 report.[4] Cases of neurologic complications associated with reactivated VZV but without rash (zoster sine herpete) in unvaccinated immunocompetent children have also been reported.[8,9]

Detection of wild-type VZV, and the absence of varicella rash history, indicate this patient had unrecognized varicella, either previously or at the time of this fatal illness. We were unable to determine whether the patient's encephalitis was because of breakthrough infection or herpes zoster. In healthy vaccinees, breakthrough varicella is usually mild. However, in this patient, we cannot exclude the possibility of an underlying immunocompromising condition, given some features of her medical history that could have led to severe breakthrough. If the patient's illness was breakthrough, its severity might also be attributable to lack of response to vaccination (ie, primary vaccine failure). Serologic studies have reported that 15%–24% of healthy children lack adequate antibody response after 1 dose of varicella vaccine, and clinical studies have revealed that approximately one-quarter of breakthrough cases have clinical characteristics similar to varicella among unvaccinated persons.[2] Waning of vaccine-induced immunity was suggested by one study[10] but not confirmed by others.[11]

In this patient, we also cannot exclude the possibility of herpes zoster. Past breakthrough disease, although not reported, could have been missed considering that the presentation is usually mild or atypical. The differential diagnosis between varicella and herpes zoster can be made clinically in most situations by assessing rash, but this patient did not have rash at presentation. No laboratory tests exist to differentiate between the 2 illnesses.

Children with acute otherwise unexplained neurologic symptoms may warrant an investigation for encephalitis, and that VZV should be considered as a possible cause of encephalitis, even if rash is not present and varicella vaccine has been received. Available tests include polymerase chain reaction to detect the viral genome in cerebrospinal fluid and assays to detect intrathecal immunoglobulin G. Biopsy can also be considered in individual cases and may aid with diagnosis. Early diagnosis improves the chance of successful treatment.

For this patient, past varicella vaccination, absence of rash and atypical neuroimaging did not raise suspicion of VZV encephalitis. To provide protection among children who do not respond adequately to the first dose of varicella vaccine and to further reduce the disease burden of varicella, a second dose of varicella vaccine is recommended for children aged 4–6 years.[2] The fact that this child was appropriately vaccinated for age may prompt consideration of earlier administration of the second dose.

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MICROSPORIDIA AND COCCIDIA AS CAUSES OF PERSISTENCE DIARRHEA AMONG LIVER TRANSPLANT CHILDREN: INCIDENCE RATE AND SPECIES/GENOTYPES

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Abstract: We determined species/genotype(s) of enteric microsporidia and coccidia causing diarrhea among 44 liver transplant children in Shiraz Nemazee hospital using acid-fast-trichrome staining and polymerase chain reaction-sequencing techniques. *Enterocytozoon bieneusi* (genotype D), *Cryptosporidium* (*parvum* and *meleagridis*) were detected in 6.81% and 11.36% of the children, respectively.

Key Words: liver, transplant recipients, children, diarrhea, microsporidiosis, Iran

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Diarrhea is common complaint after liver transplantation (LT). LT requires the use of immunosuppressive agents and broad-spectrum antibiotics in the immediate postoperative period. Consequently, the most common causes for diarrhea are infection and medication-associated side effects.[1]

Advances in surgical techniques and improvements in immunosuppression regimens have resulted in overall increased survival among LT recipients, but infection continues to be the leading cause of morbidity and mortality.

Enteric opportunistic parasites are increasingly recognized as causes of enterocolitis in humans. In immunologically competent individuals, the commonest manifestation is explosive watery diarrhea usually accompanied by vomiting, anorexia, cramping abdominal pains and low-grade fever. This is a self-limiting illness lasting 3–14 days. In immunocompromised patients, infection is characterized by intractable watery diarrhea that is resistant to antimicrobial treatment and is associated with high mortality.[2]

Of the 14 species of microsporidia identified as human pathogens, 2 species cause gastrointestinal disease, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*, with the former being the more commonly identified microsporidia in solid organ transplant recipients.[3]

The aim of the present study was to determine the incidence rate, species and genotypes of microsporidia spp. as possible causes of diarrhea among children who underwent LT and due to persistent diarrheal illness admitted to a teaching hospital of Shiraz.

MATERIALS AND METHODS

This was a prospective study during the 36 months from September 2008 to August 2011. The study population included 44 children (23 boys and 21 girls) aged 18 months–10 years with persistent diarrhea admitted to Nemazee hospital, Shiraz, Iran. These patients were receiving immunosuppressive drugs for LT at the time of study. Stool samples were collected and sent to the Parasitology and Mycology Department of Shiraz School of Medicine to detect *Cryptosporidium* as a possible cause of diarrheal illness. Whenever possible, more than 1 fecal sample was collected from each patient. A questionnaire was completed for each patient documenting clinical information such as diarrhea, animal contact, gender and age. Diarrhea was defined as the passage of watery or loose stools for at least 2 weeks. All fecal samples were investigated by light microscopy and nested-polymerase chain reactions.

Parasitologic Method

Samples were examined for larvae of *Strongyloides stercoralis*, ova of helminthes, cyst and trophozoite of protozoa by direct wet smear and formalin-ethyl acetate concentration method. The acid-fast-trichrome staining method was used to examine screen spores of microsporidia spp., *Cryptosporidium* spp., *Isospora belli* and *Cyclospora cayetanensis*.[4] After microscopic examination, stained fecal smears were stored at room temperature, and DNA was then extracted from each fecal smear with a modified protocol as described previously within 2 weeks of preparation.[5]

Gene Amplification and Sequencing

Polymerase chain reaction (PCR) analysis of small subunit ribosomal RNA (SSU-rRNA) of intestinal microsporidia was performed by using species-specific primers to identify *E. bieneusi* and *E. intestinalis* infections, respectively (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B351).[6] Nowadays, the sequencing of the internal transcribed spacer (ITS) region of the rRNA gene is regarded as the standard method for genotyping of *E. bieneusi* isolates.[7] Therefore, the PCR amplification was conducted using a set of nested primers specific for *E. bieneusi* that amplified the ITS of the rRNA gene (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B351).[8]

A 2-step nested PCR, which amplified an approximately 830 bp portion of the 18S rRNA gene of *Cryptosporidium*, was performed as previously described (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B351).[8]

For detection of *C. cayetanensis*, PCR amplification was performed on the SSU-rRNA coding region of the genome (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B351).[9]

A 2-step nested PCR protocol was used to amplify a 450 bp fragment of the ITS-1 rDNA locus of *I. belli* (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B351).[10]

Positive and negative controls were used for each PCR batch. To confirm or reject genotyping, the PCR products of the positive samples were purified using a PCR product purification kit (QIAGEN Co., Hilden, Germany) and sent to the Kawasar Tech Exploration company (Tehran, Iran) for sequencing.