Severe Postvaccinia Encephalitis with Acute Disseminated Encephalomyelitis: Recovery with Early Intravenous Immunoglobulin, High-Dose Steroids, and Vaccinia Immunoglobulin

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We report the second case of severe postvaccinal encephalitis with acute disseminated encephalomyelitis since smallpox vaccination was reintroduced in 2002. Both affected patients responded dramatically with early intervention of intravenous immunoglobulin. Our patient, who also received concurrent vaccinia immunoglobulin and corticosteroids, demonstrated full recovery.

Because of concerns about exposure to smallpox from an intentional pathogen release, the United States re instituted vaccination against smallpox among military personnel in 2002 [1] and select civilian public health care workers in 2003 [2]. Both groups have been vaccinated with the New York City Board of Health vaccinia strain (Dryvax; Wyeth Laboratories) [1, 2]. Although rare, postvaccinal encephalitis (PVE) is a potentially severe complication of smallpox vaccination. Estimates of rates of PVE vary by study, decade, country, and vaccine strain. Literature from the United States in the 1960s suggested that PVE occurs 9–59 times for every 1 million vaccinations [3]. The case-fatality rate has been reported at 25% [3]. PVE tends to occur within 2 weeks after vaccination and is 10 times more common after primary vaccination [3]. PVE has classically been subdivided into 2 clinicopathologic diseases: microglial encephalitis and a “cytotoxic” postvaccinal encephalopathy [3]. Microglial encephalitis is characterized by widespread demyelination, in particular of subcortical white matter, and likely corresponds to acute disseminated encephalomyelitis (ADEM) [3]. Cytotoxic PVE, with diffuse cerebral edema, lymphocytic meningeal infiltration, and perivascular hemorrhage, is thought to be the result of direct neuroinvasion by vaccinia, because the virus has at times been detected in samples of blood, CSF, or brain tissue from patients with PVE [3, 4].

Since the smallpox vaccine was reintroduced, 3 cases of probable PVE, including 1 with ADEM, were identified among the >700,000 vaccinees in the United States during 2002–2004 [3]. Here, we report the second case of ADEM since 2002. Common to both affected patients was early use of high-dose intravenous immunoglobulin (IVIG), an approach that differs from most conventional therapies for ADEM [5, 6]. Our patient also received vaccinia immunoglobulin (VIG) and, to our knowledge, is the first case of PVE with ADEM since the reintroduction of the smallpox vaccine in which the patient had a full recovery.

Case report. A 19-year-old male in active military service who was preparing for deployment to Iraq was admitted to a local hospital on 4 September 2007 with rapidly progressive encephalopathy. Twelve days before his hospital admission, he received a primary intradermal inoculation with vaccinia. Other recent vaccines included typhoid polysaccharide (17 days before admission) and anthrax doses 1 and 2 (17 and 5 days before admission, respectively). His past medical history was unremarkable except for a history of migraine headaches and childhood varicella. The patient began military training in Texas in November 2006 before being stationed in North Carolina in April 2007. He visited his mother in upstate New York in July 2007. His family, friends, and coworkers knew of no history of tick or mosquito bites or animal exposure. He had no known contact with ill persons.

At hospital admission, physical examination was significant for a fever of 39.4°C and altered mental status, as demonstrated by inability to follow commands and by disorientation (able only to provide the correct year). After lumbar puncture, vancomycin, ceftriaxone, and acyclovir were administered. The patient underwent intubation because of rapidly declining mental status and was transferred to North Carolina Memorial Hospital (Chapel Hill) for further care. On arrival, a 4-cm healing...
eschar was found at his vaccination site. Neurological examination revealed a comatose patient with intact brain stem reflexes, extensor posturing to nail-bed pressure, and symmetric hyperreflexia. Laboratory tests performed at hospital admission were significant for leukocytosis (WBC count, \(12.2 \times 10^3\) cells/mm\(^3\)) with an elevated absolute neutrophil count (10.7 \(\times 10^3\) cells/mm\(^3\)). Analysis of a CSF sample revealed a lymphocytic pleiocytosis, with 125 WBCs/mm\(^3\) (59% lymphocytes, 28% neutrophils, and 13% monocytes) and 3 RBCs/mm\(^3\). CSF protein and glucose levels were 65 mg/dL and 91 mg/dL, respectively. Gram stain revealed no organisms. CSF and serum samples were sent to the Centers for Disease Control and Prevention (CDC) for further testing.

MRI of the brain (figure 1A) with and without gadolinium on day 2 revealed large areas of abnormal T2-weighted and fluid-attenuated inversion recovery signal involving subcortical and deep white matter within the bilateral frontal, parietal, occipital, and medial temporal lobes; right thalamus; corpus callosum; and periventricular white matter. There was also abnormal fluid-attenuated inversion recovery within the subarachnoid space.

Ampicillin and doxycycline were added to the patient’s antibiotic regimen. On the basis of the criteria of Sejvar et al. [3], the clinical impression was of probable PVE with ADEM. High-dose methylprednisolone (500 mg every 12 h) was started on hospital day 2, and IVIG (30 g per day) was started on day 3. On hospital day 3, the CDC reported that the patient’s CSF and serum samples were negative, by PCR, for orthopoxvirus DNA but that the CSF sample was positive for orthopoxvirus IgM, although negative for IgG; the serum sample was positive for orthopoxvirus IgM and IgG. CSF viral cultures at the CDC remained negative. On the advice of the CDC and the Department of Defense’s Vaccine Healthcare Centers Network, the patient received 1 dose of 400,000 units of intravenous VIG on day 4. The patient received IVIG for 5 days; high-dose methylprednisolone was continued for 5 days and was tapered over 8 days, followed by oral prednisone, for 35 days of total steroid therapy. Antibiotics and antivirals were discontinued after results of cultures of CSF were negative and PCRs were negative for herpes simplex virus 1 and 2 and varicella-zoster virus.

Additional negative results of tests performed on CSF samples included mycobacterial and fungal cultures, cryptococcal antigen, Venereal Disease Research Laboratory test for syphilis, Lyme antibody, arbovirus antibodies (i.e., West Nile, eastern equine, western equine, St. Louis encephalitis, and Lassa viruses), and PCR for enterovirus, cytomegalovirus, Epstein-Barr virus, adenovirus, and human herpesvirus 6. CSF samples were negative for oligoclonal bands. Negative serum or plasma laboratory tests included HIV by ELISA and PCR, Rapid Plasma Reagin, Epstein-Barr virus DNA, Rocky Mountain spotted fever, and arbovirus serologies. Cytomegalovirus PCR revealed <250 copies/mL. Epstein-Barr virus serologies were consistent with past infection. Complement levels (total, C2, C3, and C4), C1q binding, and C3-D binding assays were normal. The patient did not have detectable circulating immune complexes. Broadly reactive viral family PCRs tested by the CDC on total nucleic acids extracted from CSF on hospital day 1 were found to be negative for flaviviruses, alphaviruses, bunyaviruses, adenoviruses, coronaviruses, polyomaviruses, bornaviruses, paramyxoviruses, and rhabdoviruses. A pan herpesvirus PCR, performed at the CDC, was positive, and subsequent sequencing revealed human herpes virus 7 (HHV-7). Semiquantitative real-time PCR revealed low-level HHV-7 (<650 copies/mL). However, CSF from day 9 was negative for HHV-7 by pan herpesvirus PCR, and serum from hospital days 1 and 6 showed no evidence of HHV-7 infection with IgG (\(<:1:40\) and \(<:1:160\), respectively) or IgM (\(<:1:40\)).

The patient’s initial recovery was gradual. He began to track with his eyes by day 8. By day 13, he underwent extubation, and his neurologic recovery accelerated. Although still weak and with a hoarse voice, the patient was able to walk independently when he was discharged from the hospital on day 37. Three months after his illness, he had returned to active duty.

**Figure 1.** Fluid-attenuated inversion recovery image from MRIs on day 1 (A), which demonstrates multiple high-signal lesions involving predominantly the white matter and corpus callosum, on day 8 (B), which shows progression of bilateral lesions involving the white matter, basal ganglia, and the corpus callosum, and 4 months later (C), which demonstrates nearly complete resolution of signal abnormalities.
with minor restrictions. At his 4-month follow-up appointment, he noted an occasional involuntary right shoulder droop and a reproducible numbness and tingling over the dorsal aspect of his left hand only when pressure was applied to that hand. On examination, he demonstrated no neurological deficits. His follow-up MRI showed near-complete resolution of his prior lesions (figure 1A–1C). By month 7, he had been cleared for duty.

Discussion. We believe that our patient had the second documented case of severe PVE with ADEM since the reintroduction of the smallpox vaccine in 2002. Our patient was unique in that his CSF was tested and was found to be IgM positive for orthopoxvirus. Although we do not believe that our patient experienced neuroinvasive vaccinial encephalitis, his positive IgM status raises the possibility that our patient may have had a paravaccinial encephalitis [6] rather than PVE.

Both patients, although initially comatose and paralyzed, made dramatic recoveries. Both received IVIG. The first patient, who proved to be steroid resistant (after 5 days of therapy), was treated with single-bolus high-dose (2 g/kg) IVIG. His only residua are mild lower-extremity weakness and detrusor dyssynergia [5]. Our patient, who received concurrent methylprednisolone, IVIG, and VIG, recovered sufficiently to return to full active duty. Earlier initiation of IVIG therapy (day 3 vs. day 7) is suggestive of additional benefit, although its significance cannot be fully assessed because of the small number of cases.

The therapy for ADEM after immunization with vaccines such as measles and vaccinia remains controversial, because the rarity of the disorder precludes assessing the efficacy of interventions through use of a randomized clinical trial. Limited post-MRI literature about untreated ADEM and older literature describing postimmunization encephalitis depict outcomes that range from complete recovery without specific therapy to reports of mortality rates as high as 25%–50% [3, 7, 8]. Thus, therapy decisions must be based on expert opinion and anecdotal reports. In our case, it is not possible to determine whether the patient would have fully recovered without any intervention or to determine the relative contributions of steroids, IVIG, and VIG.

Although ADEM pathogenesis is not fully understood, PVE with ADEM is clearly an immune-mediated disease [5, 6, 7]. Our case, taken together with the case reported by Fu and Montgomery [5], bolsters the argument for prompt initiation of IVIG for patients with PVE and ADEM. For refractory cases, plasma exchange may also be considered [7]. Although VIG has shown efficacy in prophylaxis against PVE, it has not previously been effective as therapy for PVE [9]. Our case suggests that VIG might be a helpful adjunct.

As of December 2007, >1.4 million military personnel have been vaccinated against smallpox at >1000 clinic sites worldwide (R. Engler, personal communication). For this reason, it is critical that local physicians be able to rapidly recognize this rare but potentially life-threatening complication of smallpox vaccination. Our case underscores the utmost importance of a coordinated multidisciplinary approach, with close consultation with the Department of Defense’s Vaccine Healthcare Centers Network and the CDC for cases of suspected PVE. Rapid access to specialized laboratories and expert consultation across multiple institutions facilitated thorough and timely decisions about treatment management that we believe led to a favorable outcome for our patient.

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