A smallpox vaccination program has been initiated. The vaccine is a live virus that was used in the last century. Postvaccinal encephalitis is a complication of this vaccine. The clinical presentation, course, neuroimaging findings, and spinal fluid abnormalities are similar to a disorder that physicians are familiar with, acute disseminated encephalomyelitis. This complication can be prevented with the administration of antivaccinia gamma globulin at the time of vaccination. Antivaccinia gamma globulin is not efficacious once this complication occurs. Intravenous methylprednisolone is the recommended therapy, although intravenous immunoglobulin and plasmapheresis should be investigated in the treatment of postvaccinal encephalitis.

The worldwide eradication of smallpox, certified in 1980, is one of the greatest public health achievements in history. Smallpox was a highly contagious, painful, and disfiguring disease. The Fifty-second World Health Assembly, May 17-25, 1999, in Geneva, Switzerland, reaffirmed the decision of previous assemblies authorizing the temporary retention of remaining stocks of variola virus in 2 designated laboratories, one at the Centers for Disease Control and Prevention in Atlanta, Ga, and the other at the Institute for Viral Preparations in Novosibirsk, Russia. Virus was retained in these laboratories to develop a safer smallpox vaccine, should the disease reappear. The virus was then to be destroyed. The Pentagon has had a program to develop a new smallpox vaccine, but this vaccine will not be available until 2004. The present concern is that smallpox virus will be procured and used as a weapon of bioterrorism. On January 24, 2003, vaccination programs were begun using the old Dryvax vaccine that was used in the last century. This is a live virus vaccine. There are several complications of the Dryvax vaccine, including postvaccinal encephalitis (PE). The clinical presentation and treatment of this complication will be reviewed to prepare physicians, should they need to care for patients with this disease.

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HISTORY

Smallpox is believed to have appeared at the time of the first agricultural settlements in northeastern Africa, around 10000 BC. It is thought to have caused epidemics in Egypt, as skin lesions resembling those of smallpox were found on the faces of mummies, and in ancient Athens in 430 BC. In the New World, smallpox was also likely responsible for the extermination of the Aztec and Inca empires. Many famous people in history were affected by the disease, including Mozart, Beethoven, Queen Elizabeth I of England, George Washington, Abraham Lincoln, and Joseph Stalin.

To induce immunity to smallpox, fluid from pustules or ground-up material from dried smallpox scabs from patients in whom the disease had been benign was inoculated into healthy susceptible persons. In 1796, Edward Jenner, inspired by reports that milkmaids and dairy farm workers who previously contracted cowpox were protected from smallpox, inoculated an 8-year-old boy with fluid from a cowpox pustule from the hand of a milkmaid. When the boy was subsequently exposed to smallpox, he was resistant to infection. The idea of preventing disease by challenging the immune system with an altered, less virulent agent was a milestone in medical history. The
name vaccination, derived from the Latin vaca (cow), was given to this procedure.4,7

President Thomas Jefferson was a strong advocate of the smallpox vaccine and established the National Vaccine Institute to begin widespread smallpox vaccination in the United States. In 1806, Jefferson wrote a congratulatory letter to Jenner: “Future generations will know by history only that the loathsome smallpox existed and by you has been extirpated.”8 One of the earliest descriptions of postinfectious encephalitis is recorded in 1790. A 23-year-old woman developed symptoms of encephalitis following smallpox and transverse myelitis following measles.9 From 1853 to 1896, the complications of generalized vaccinia and convulsions in infants during the fever of smallpox were recognized, but nothing resembling the condition we now call postvaccinal encephalitis was reported.10,11 In 1905, a case of encephalitis after the jennerian cowpox inoculation was reported in France, and another case was observed in the London Hospital in 1912.12 In 1922, 11 fatalities due to PE were reported in Great Britain, and this complication was recognized from this time onward.11

INCIDENCE

Postvaccinal encephalitis is an acute monophasic disorder of the central nervous system characterized by multifocal inflammatory and demyelinating lesions following vaccination.10 Most cases occur 7 to 14 days after vaccination, but cases have been reported as early as 1 day and as late as 23 days following vaccination.13 Vaccination was done before the first birthday if there was a reasonable chance that a child would come in contact with smallpox. The risk of PE increased directly with increasing age of primary vaccination after the first year of life.14

Complications occur at least 10 times more frequently in primary vaccinees than in revaccinees.15 Complications in revaccinees occur in individuals who have not been vaccinated for many years, and therefore react like primary vaccinees, and in individuals who have acquired immunodeficiency disorders.13

The incidence of PE varied among countries. In New York City during the smallpox outbreak in 1947 and ring vaccination programs, the reported incidence was 1 in 100,000.11 In 1968, 5994000 primary vaccinations and 857400 revaccinations were done in the United States. The overall incidence of PE was 2.9 per 1 million primary vaccinations.16 None of the revaccinees developed PE. The case fatality rate of PE between 1959 and 1966 was approximately 25% in the United States17 and 30% to 50% in Europe.18 The incidence of PE per 100,000 vaccinations in different European countries in 1964 is given19:

<table>
<thead>
<tr>
<th>European Countries</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Britain</td>
<td>1.5</td>
</tr>
<tr>
<td>Finland</td>
<td>3.1</td>
</tr>
<tr>
<td>Sweden</td>
<td>3.5</td>
</tr>
<tr>
<td>Switzerland</td>
<td>5.0</td>
</tr>
<tr>
<td>Belgium</td>
<td>7.0</td>
</tr>
<tr>
<td>Holland</td>
<td>13.0</td>
</tr>
<tr>
<td>Germany</td>
<td>11.0</td>
</tr>
<tr>
<td>Austria</td>
<td>30.0</td>
</tr>
</tbody>
</table>

The basis for these differences in attack rates has never been clarified but could reflect differences in the genetic susceptibility in different populations. There has been no correlation of the incidence of encephalitis with the source of the vaccine, the neurotropism, or the antigenicity of the virus in the vaccine.21

The concern in 2003 is that there will be a greater incidence of PE because of the number of immunosuppressed individuals from human immunodeficiency virus infection, organ transplantation, chronic illness, and cancer and immunosuppressive therapies.

IMMUNITY PRODUCED BY VACCINATION

Recently, suspicions that strains of smallpox virus may be held somewhere else to be used as biological weapons have given rise to preparations for mass vaccination programs.10 Vaccination provides almost complete protection against smallpox, but periodic revaccination is necessary to guarantee that adequate immunity is maintained. Successful vaccination in the 2 to 3 years before exposure reduces the attack rate to less than 10% and the mortality to less than 1%. Postexposure vaccination, in the first 4 days after exposure, can reduce the attack rate by 24% to 50%.2

Immunity against the vaccinia virus depends on cellular immunity and circulating antibodies.20 Vaccinia virus replicates at the site of inoculation and disseminates to regional lymph nodes. Viremia does not regularly occur after uncomplicated primary vaccination, but in vaccinees who developed encephalitis, virus was found in blood and cerebrospinal fluid between 10 and 35 days after vaccination.21

Following classic intradermal primary vaccination, antibodies can be detected within 5 days, increasing in titer for 2 to 4 weeks thereafter. Antibodies may persist for several years.

T-cell immune responses are important in the immunologic reaction to smallpox and to the vaccinia vaccine. Children with congenital T-cell immunodeficiency disorders and adults with acquired T-cell immunodeficiency have serious, and at times fatal, infections when vaccinated. Little is known about the induction of human vaccinia virus–specific CD4+ and CD8+ cytotoxic T lymphocytes following vaccination, although it has been recently reported that, after stimulation of peripheral blood mononuclear cells with live vaccinia virus, the vaccinia virus–specific interferon γ-producing T cells were predominantly CD8+.22

The replication of substantial amounts of vaccinia virus within pox lesions at the injection site may be required for the induction of cytotoxic T-lymphocyte memory responses in recipients of standard smallpox vaccine and optimal induction of virus-specific interferon γ-producing T cells.22 The administration of a more attenuated recombinant vaccinia virus to a vaccinia virus–immune person may be enough to generate immune protection against the virus, with a lower risk of secondary effects.

MECHANISMS OF PATHOGENESIS OF PE

The central nervous system is relatively isolated from systemic immune responses in the absence of disease. Only a small number of lymphocytes are found in normal cerebrospinal fluid. Two resident neural cell types play a
role in immune responses: the pericytes, or perivascular macrophages, and the microglia.20

An immune pathogenesis in the development of PE is supported by the evidence that there is a period of time between vaccination and encephalitis, suggesting that an inciting event activates the immune system. In addition, there are similarities between the neuropathologic abnormalities of PE and those of animal models of experimental allergic-autoimmune encephalitis.

There are approximately 7 days between the inoculation of the antigen and the onset of the postinfectious syndrome. During this time, there is an interaction between the virus and the immune system that is detrimental to the host.19 Vaccinia virus and other poxviruses express proteins that neutralize host cytokines, chemokines, and interferons.21 In addition, vaccinia virus induces apoptosis of infected macrophages, which leads to a deficiency of cytokines produced by macrophages, thus altering the immune response mediated by T cells.24

Acute demyelinating encephalomyelitis and acute hemorrhagic leukoencephalitis have been described in patients with PE, which may represent a gradient of severity of the same disease.11 Acute demyelinating encephalomyelitis (also called acute disseminated encephalomyelitis and parainfectious encephalomyelitis) is characterized neuropathologically by perivascular lymphocytic and mononuclear cell infiltration and perivascular demyelination. Acute hemorrhagic leukencephalitis is a hyperacute and fulminating disorder characterized neuropathologically by polymorphonuclear cell perivascular infiltrate and multiple small hemorrhages in the white matter. These 2 presentations share similarities with that of experimental allergic encephalitis.

Experimental allergic encephalitis is an autoimmune disease of the central nervous system mediated by T cells specific for myelin antigens. The role of myelin basic protein as the antigen responsible for the induction of experimental allergic encephalitis is well established, but the events leading to myelin destruction in PE are not clear.25 A vaccinia virus kinase can phosphorylate myelin basic protein in the myelin membrane in vitro, producing phosphorylated peptides that are different from the peptides phosphorylated by the endogenous myelin protein kinase. The phosphate residues of myelin basic protein that were introduced by the viral kinase may change the immunogenicity of host proteins, resulting in demyelination.20

There is evidence that a neurotropic strain of vaccinia virus (strain WR) is able to elicit an immunologic reaction that appears to be directed toward the myelin-oligodendrocyte compartment. Mice injected with WR develop a high titer of antemyelin and antigalactocerebroside (a cell surface marker for oligodendrocytes) antibodies.27 In addition, WR encodes a 43-kDa glycoprotein that is secreted from infected cells early in infection and is able to inhibit interferon from a wide range of species and increase the virulence of the virus.28

NEUROLOGICAL SYNDROMES ASSOCIATED WITH SMALLPOX VACCINE

Several neurological syndromes have been described in association with the smallpox vaccine. Symptoms of headache, fever, mild photophobia, and nuchal rigidity have developed between 5 and 7 days after vaccination concomitantly with the vaccine viremia. Febrile convulsions occurred in young children during the febrile response to vaccination. The seizures fulfilled the definition of febrile convulsions of childhood.29 Beginning 1 week after vaccination, infants and children younger than 2 years old had a brief period of irritability followed by a generalized, prolonged seizure, which resulted in coma. In most children, recovery was rapid and complete, with total return of function within 24 to 48 hours, but some children died.29,30

The symptoms of PE developed between 8 and 15 days after vaccination. There was a progressive deterioration in the level of consciousness from irritability or lethargy to obtundation and coma in most cases. Movement disorders, tremor, ataxia, convulsions, and signs of pyramidal tract disease have been described. Spinal fluid analysis revealed a lymphocytic pleocytosis, an increased protein concentration, and a normal glucose concentration.28 Death usually occurred within 48 hours of the onset of coma. Survivors had minimal or no neurological sequelae.29

PROPHYLAXIS AND THERAPY

The plan before September 11, 2001, was to mitigate the possible adverse reactions to the Dryvax smallpox vaccine by developing a safer vaccine. Since September 11, there has been growing concern that smallpox will be used in a bioterrorism attack. On January 24, 2003, vaccination programs began in the United States. As the number of vaccinees increases, patients with PE may present to the emergency department.

At the present time, the only agent with proven efficacy in the prevention of PE is antivaccinia gamma globulin (AGG). The incidence of PE is significantly decreased by the administration of intravenous AGG at the time of vaccination.31-33 Antivaccinia gamma globulin is obtained from healthy individuals who have recently been vaccinated. Intravenous immunoglobulin may be similar effective in the prevention of PE. It contains a vast array of anti-idiotypic antibodies. One of the most salient characteristics of anti-idiotypic antibodies is their ability to neutralize lymphokines, such as tumor necrosis factor and soluble intercellular adhesion molecule 1, substances involved in the pathogenesis of experimental allergic encephalitis.32 Intravenous AGG was not effective in the therapy of PE once this complication occurred.33,34 It is not known if intravenous immunoglobulin therapy would be effective.

Cidofovir, an antiviral drug that is used in the treatment of human cytomegalovirus retinitis in immunocompromised patients, is an acyclic nucleoside phosphonate analogue that selectively inhibits the viral DNA polymerase.35 Cidofovir has proven effective against vaccinia in animal model infections and has demonstrated activity against variola virus in cell culture.35 Cidofovir confers a pronounced and prolonged inhibition of vaccinia viral replication in vitro as early as 6 hours after infection that lasts for at least 7 days after treatment with the drug.36 Cidofovir may be an effective alternative to
smallpox vaccination. Adverse effects of cidofovir include nephrotoxicity, neutropenia, rashes, and gastrointestinal intolerance. Hydroxyethylene diphosphonate cidofovir is the lipid prodrug of cidofovir that can be administered orally.

The therapeutic management of a patient with PE should be similar to that presently used for parainfectious encephalomyelitis. The clinical presentation, neuropathologic abnormalities, and neuroimaging findings are similar between PE and parainfectious encephalomyelitis. Several studies suggest the efficacy of treatment with intravenous corticosteroid therapy in these patients. Methylprednisolone may be given in a dosage of 1 g/d intravenously for 3 to 5 days. Alternatively, intravenous methylprednisolone may be given in a dosage of 1000 mg/d for 5 days, followed by 500 mg/d for 3 days and then 250 mg/d for 3 days. Either course of methylprednisolone may be followed by a 4- to 8-week course of tapering dosages of oral prednisone. Plasmapheresis has been used in the treatment of acute disseminated encephalomyelitis, but its efficacy in PE is unknown. Given the present understanding of the pathogenesis of PE and the role of T cells, plasmapheresis is not likely to be efficacious.

CONCLUSIONS

The diagnosis of PE is made in the patient who has been vaccinated with the smallpox vaccine 8 to 15 days before the onset of symptoms of an altered level of consciousness, movement disorders, and convulsions, with multifocal demyelinating lesions seen on magnetic resonance imaging and a cerebrospinal fluid lymphocytic pleocytosis with a normal glucose concentration. Intravenous methylprednisolone is most likely the best initial therapy. Historically, intravenous AGG was not efficacious in the treatment of PE once this complication occurred, so intravenous immunoglobulin may similarly not be effective, but this should be investigated further.

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