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Guillain-Barré Syndrome Among Recipients of Menactra® Meningococcal Conjugate Vaccine — United States, June–July 2005

On January 14, 2005, a quadrivalent (A, C, Y, and W135) meningococcal conjugate vaccine (Meningococcal Polysaccharide Diphtheria Toxoid Conjugate Vaccine, Menactra®, Sanofi-Pasteur, Swiftwater, Pennsylvania) (MCV4) was licensed in the United States. MCV4 is a tetravalent vaccine; each 0.5-mL dose contains 4 μg each of capsular polysaccharide from *Neisseria meningitidis* serogroups A, C, Y, and W-135 conjugated to 48 μg of diphtheria toxoid. In February 2005, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of adolescents at the preadolescent health-care visit (at ages 11–12 years) (*1*). For persons who have not been vaccinated previously, ACIP recommended vaccination before high-school entry (at approximately age 15 years). Routine vaccination also is indicated for first-year college students living in dormitories and for other persons at increased risk.*

As of October 4, 2005,† the Vaccine Adverse Event Reporting System (VAERS) received five reports of Guillain-Barré syndrome (GBS) in persons after receipt of MCV4 vaccination. VAERS, operated by CDC and the Food and Drug Administration (FDA), is a national passive surveillance system that monitors the safety of vaccines (*2*). Health-care providers, state and local health departments, consumers, and vaccine manufacturers are encouraged to report adverse events involving all U.S.-licensed vaccines. All five persons had been vaccinated during June 10–July 25. This report describes the clinical and epidemiologic features of these five cases and summarizes preliminary data from ongoing studies.

Case Reports

Case 1. A male aged 18 years was vaccinated with MCV4; 15 days later, he experienced tingling in his feet and hands. He had no history of major underlying illness; his mother had had GBS 5 years earlier. He reported no history of respiratory or gastrointestinal illnesses during the 6 weeks before onset of symptoms. Sixteen days after vaccination, he was hospitalized, and nerve conduction studies (NCS) of upper and lower extremities, 2 days after onset of symptoms, were consistent with GBS. He was observed for 3 days, discharged, and then readmitted 2 days later with bilateral facial weakness and increasing lower extremity weakness. Patellar, triceps, and biceps deep tendon reflexes (DTRs) were absent. NCS performed 4 days after the previous examination revealed worsening motor nerve conduction velocities consistent with GBS. Tests for mononucleosis and Lyme disease were negative. During hospitalization, he was treated with plasmapheresis. His facial palsy and gait improved, and his reflexes returned. He was discharged home.

Case 2. A male aged 17 years was vaccinated with MCV4; approximately 25 days later, he had difficulty walking, followed by difficulty moving from a standing to a seated position. Medical history included attention deficit hyperactivity disorder and Asperger syndrome; he had been taking multiple psychotropic medications. He did not report recent respiratory or gastrointestinal illness. Thirty-two days after vaccination, he was hospitalized with bilateral muscle weakness of upper and lower extremities with absent DTRs. NCS was consistent with GBS. Cerebrospinal fluid (CSF) analysis revealed 2 white blood cells (WBC)/mm^3 with protein of 60 mg/dL; bacterial cultures were negative. DNA polymerase chain reaction (PCR) for adenovirus, herpes simplex virus types 1 and 2, varicella zoster virus, cytomegalovirus (CMV), and Epstein-Barr virus (EBV), and RNA PCR for West Nile virus, eastern equine encephalitis virus, St. Louis encephalitis virus, enterovirus, and California group and Cache Valley viruses, were all negative. During hospitalization, he was treated with intravenous immunoglobulin (IVIG). On discharge, his motor strength and gait were improved.

*Military recruits, travelers to areas in which meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of *N. meningitidis*, patients with anatomic or functional asplenia, and patients with terminal complement deficiency

†A sixth report of a possible case was received on October 4 and is currently being investigated.

Case 3. A female aged 17 years was vaccinated with MCV4. She had a previous history of GBS at ages 2 and 5 years, both beginning 14 days after vaccination with childhood vaccines. She had not been previously vaccinated with meningococcal vaccine. Both episodes of GBS were characterized by muscle weakness, decreased reflexes, and difficulty walking. During both episodes, she was treated with intravenous immunoglobulin and completely recovered. Fourteen days after vaccination with MCV4, she reported numbness of toes and tongue and had a lump in her throat. These symptoms were followed by numbness of thighs and fingertips, arm weakness, inability to run, difficulty walking, and falling. Sixteen days after vaccination, she was hospitalized, and neurologic examination revealed decreased tone and weakness of both arms and legs and reflexes reduced or absent in ankles, knees, and arms. CSF results revealed 0 WBC/mm^3 and protein 26 mg/dL. She was treated with IVIG, recovered, and discharged home.

Case 4. A female aged 18 years was vaccinated with MCV4. Six days after vaccination, she had a sore throat that lasted for 6 days, and 29 days after vaccination she reported a severe headache and was evaluated in an emergency department (ED), where she had a normal computerized tomography (CT) scan, was treated with ketorolac, and discharged on oral ibuprofen. Thirty-one days after vaccination, the patient reported numbness of legs and had trouble standing on her toes. The next morning she could not stand. The patient was admitted to the hospital, and physical examination revealed decreased muscle strength in ankles and wrists bilaterally and reduced biceps, knee, and ankle DTRs. Previous medical history included mild ulcerative colitis that had been asymptomatic off medications; she did not report having diarrhea during the 6 weeks before onset of muscle weakness. Her only outpatient medications were oral contraceptives. CSF analysis revealed 1 WBC/mm^3 and a protein concentration of 30 mg/dL. NCS was consistent with GBS. She was treated with IVIG. After a 7-day hospitalization, her motor strength had improved, and she was discharged home with outpatient physical therapy. Three weeks after discharge, her weakness and gait were improved.

Case 5. A female aged 18 years was vaccinated with MCV4; 14 days later, she experienced heaviness in her legs when walking upstairs. During the next 8 days, her difficulty walking continued, and she had bilateral leg pain. Subsequently, she reported headache, back and neck pain, vomiting, and tingling in both hands. She became unable to walk and was evaluated in an ED, where an initial diagnosis of viral meningitis was made. Two days later, she was hospitalized for progressive weakness and inability to walk. Neurologic examination revealed bilateral acute flaccid weakness with decreased DTRs.

The woman had traveled to Portugal during the week before onset of symptoms and had a history of seasonal allergies and sinusitis, but she reported no history of respiratory, gastrointestinal, or other febrile illnesses during the 3 months before onset. CSF examination revealed 5 WBC/mm^3 and protein concentration of 177 mg/dL. Viral and bacterial cultures of CSF were negative. EBV IgM, CMV IgM, ELISA serology for Lyme disease, and serologic testing for syphilis were all negative. Electrodiagnostic studies were consistent with GBS. Treatment included plasmapheresis and IVIG. Weakness progressed to include paralysis of arms, difficulty swallowing, and respiratory compromise. She required intubation for 1 week. She was discharged to a rehabilitation facility, and 53 days after onset, she had recovered the ability to talk, feed herself, sit, and stand.

Case Summary

All reported GBS cases occurred among persons aged 17–18 years who were vaccinated during June 10–July 25 and had symptom onset 14–31 days after MCV4 vaccination. On the basis of information obtained to date, one patient reported another acute illness before onset of neurologic symptoms. The five patients described in this report received vaccine from four different lots. These cases were reported from Pennsylvania (two), New York, Ohio, and New Jersey (one case each).

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Editorial Note: GBS is a serious neurologic disorder involving inflammatory demyelination of peripheral nerves (*3*). It can occur spontaneously or after certain antecedent events such as infections. Illness is typically characterized by the subacute onset of progressive, symmetrical weakness in the legs and arms, with loss of reflexes. Sensory abnormalities, involvement of cranial nerves, and paralysis of respiratory muscles also can occur. A small proportion of patients die, and 20% of hospitalized patients can have prolonged disability. *Campylobacter jejuni*, which causes bacterial gastroenteritis, especially in young adults and during the summer months, is one identified precipitating factor for GBS.

Approximately 2.5 million doses of MCV4 have been distributed nationally since March 2005 (Sanofi-Pasteur, unpublished data, 2005). The number of exact vaccine doses administered is unknown. The precise rate of GBS also is unknown. Data from the Vaccine Safety Datalink (VSD), a collaborative project between CDC and eight managed care organizations in the United States (*4*), and the Health Care Utilization Project on GBS incidence in persons aged 11–19

years indicate a background annual incidence of 1–2 cases per 100,000 person-years (CDC; Healthcare Utilization Project Nationwide Inpatient Sample; Agency for Healthcare Research and Quality, unpublished data, 1989–2001). This finding suggests that the rate of GBS based on the number of cases reported within 6 weeks of administration of MCV4 is similar to what might have been expected to occur by chance alone. However, the timing of the onset of neurologic symptoms (i.e., within 2–5 weeks of vaccination) is of concern. In addition, the extent of underreporting of GBS to VAERS is unknown; therefore, additional cases might be unreported (*5,6*).

Prelicensure studies conducted by Sanofi Pasteur of approximately 7,000 recipients of MCV4 revealed no GBS cases (*7*). CDC has conducted a rapid survey by using available VSD and other health-care–organization databases. No cases of GBS have been detected among nearly 110,000 MCV4 recipients represented in these databases. Data from two VSD sites indicated that 86%–97% of vaccine recipients had 6 weeks of follow-up via automated data collection. These data do not rule out an association between MCV4 and GBS.

During 1999–2005, a total of 30 million doses of three different meningococcal C conjugate vaccines (MenC), with either diphtheria CRM (nontoxic variant of diphtheria toxin) or tetanus toxoid as carrier proteins, have been used in the United Kingdom (UK) for persons aged <18 years. Five cases of GBS were reported in the UK after administration of MenC vaccines (UK Department of Health, unpublished data, 2005). This reported number of cases is lower than would have been expected to occur by chance in a population this age.

To date, evidence is insufficient to conclude that MCV4 causes GBS. An ongoing known risk for serious meningococcal disease exists. Therefore, CDC is recommending continuation of current vaccination strategies. Whether receipt of MCV4 vaccine might increase the risk for recurrence of GBS is unknown; avoiding vaccinating persons who are not at high risk for meningococcal disease and who are known to have experienced GBS previously is prudent.

FDA and CDC are alerting health-care providers to this preliminary information and are actively investigating the situation because of its potentially serious nature. The manufacturer has sent letters to health-care providers and is updating the package insert to reflect that GBS has been reported in association with the vaccine. CDC recommends that adolescents and their caregivers be informed of this ongoing investigation as part of the consent process for vaccination with Menactra.

FDA and CDC are requesting that providers or other persons with knowledge of possible cases of GBS (or other clinically significant adverse events) occurring after vaccination with MCV4 report them to VAERS. Reports of GBS should be submitted to VAERS at http://www.vaers.hhs.gov or by telephone at 800-822-7967. CDC further requests that health-care providers report other cases of GBS that occur among persons aged 11–19 years to state health departments in accordance with state or local disease-reporting guidelines. CDC suggests that state health departments consider enhancing surveillance for GBS in adolescents to assist in answering these critical questions. Cases of meningococcal disease should be reported to state health departments and, if available, information on vaccination status should be provided; isolates should be saved and sent to state health departments for serogroup identification.

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