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Case report

Longitudinal myelitis associated with yellow fever vaccination

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Severe adverse reaction to yellow fever (YF) vaccine includes the yellow fever vaccine–associated neurotropic disease. This terminology includes postvaccinal encephalitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome. The objective of this communication is to report a patient who received a YF vaccine in Argentina and subsequently developed longitudinal myelitis with a symptom that had previously gone unreported in the literature. A 56-year-old man began with progressive paraparesia, urinary retention, and constipation 48 h previous to admission. The patient received YF vaccine 45 days prior to the onset of the symptoms. There was no history of other immunization or relevant condition. MR of the spine showed longitudinal intramedullary hyperintense signal (D5–12) without gadolinium enhancement. A high concentration of YFV-specific IgM vaccine antibody was found in the cerebrospinal fluid (CSF). Serological tests for other flavivirus were negative. A diagnosis of longitudinal myelitis without encephalitis associated with YF vaccine was performed and symptoms improved 5 days later. This is the first report dealing with longitudinal myelitis as a serious adverse event associated with YF vaccination in which confirmation of the presence of antibodies in CSF was found. To date, it is also the first report with serological confirmation in Argentina and in South America. We consider that the present investigation will raise awareness in the region in the reporting of adverse events related to YF vaccine and improve our knowledge of adverse reactions to the vaccine. *Journal of NeuroVirology* (2009) **15,** 348–350.

Keywords: yellow fever; vaccine; South America; neurological adverse events; myelitis

Introduction

Yellow fever (YF) is an acute viral illness caused by a mosquito-borne flavivirus. The disease is an important cause of hemorrhagic illness, which is potentially fatal in many African and South American countries (Sanders *et al,* 1998). Currently, there is no specific treatment for the illness; however, the disease can be prevented by immunization with a vaccine that is indicated in travellers and residents of endemic areas (Cetron *et al,* 2002).

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The vaccine consists of a live, but attenuated, virus known as 17D. The 17D vaccine has been used for more than 70 years (Monath, 2004) and has been described as a very safe vaccine with few mild adverse reactions reported. Nonetheless, severe adverse reaction to YF vaccine exists and includes yellow fever vaccine–associated neurotropic disease (YF-AND) (Kitchener, 2004). This terminology includes postvaccinal encephalitis, acute disseminated encephalomyelitis (ADEM), and Guillain-Barré syndrome (McMahon *et al,* 2007). Mild adverse reactions occur 5 to 7 days after vaccination, and severe reaction to YF vaccine is characterized by onset 7 to 21 days after vaccination.

The aim of this communication is to report a patient who received a YF vaccine in Argentina and subsequently developed longitudinal myelitis with a symptom that had previously gone unreported in the literature.

Case

A previously healthy 56-year-old man presented progressive paraparesia, urinary retention, and constipation that began 48 h previous to the admission. He also complained of numbness and paresthesias of lower limbs. The patient, who had to travel to an endemic YF zone of South America, received YF vaccine (Yf-Vax manufactured by Sanofi Pasteur, prepared by culturing the 17D-204 strain of yellow fever virus in living avian leucosis virus–free chicken embryos) 45 days prior to the onset of the symptoms. There was no history of other immunization or relevant disease condition. Also, there was no history of neurological disease in all his relatives. On examination, the patient had symmetric proximal weakness of the lower extremities, sensory level on D8 and normal deep tendon reflex. Cranial nerves, cerebellum, and sensor motor examination of upper limbs were normal. Other systemic examinations showed normal. An magnetic resonance (MR) scan of the spine showed longitudinal intramedullary hyperintense signal (D5–12) without gadolinium enhancement (Figure 1). Brain MR was normal. Cerebrospinal fluid (CSF) examination showed pleocytosis (110 white blood cells [WBC]/mm^3, 90% lymphocytes) and elevation of protein concentration (56 proteins/mm^3). CSF glucose was normal and microbiologic culture did not reveal bacterial or viral infection (enteroviruses, herpes simplex virus, herpes 6 virus, and varicella-zoster virus). Serological tests were negative for human immunodeficiency virus (HIV), human T-lymphotropic virus (HTLV), Venereal Disease Research Laboratory (VDRL) test, and for acute cytomegalovirus, Epstein-Bar virus, *Chlamydia*, and *Mycoplasma* infections. Subsequent autoantibody screen, lupus anticoagulant, antinuclear, and anticardiolipin antibody were negative. Anti-Neuromyelitis optica-IgG (xx–immunoglobulin G) antibodies were not tested. Considering the clinical case, complementary findings, and history of the patient, a serious adverse reaction to YF vaccine was considered and a screening for YF vaccine–specific IgM by enzyme-linked immunosorbent assay (ELISA) antibody was performed to clarify the pathogenesis of the longitudinal myelitis. After the analysis, a high concentration of YF vaccine antibody was found in the CSF. Serological tests for other South American flavivirus were performed and all results were negative. The diagnosis after the observations was for longitudinal myelitis without encephalitis associated with YF vaccine. Symptoms began to improve 5 days after admission. Currently, the patient is undergoing physical rehabilitation with significant improvement in the strength of his lower limbs.

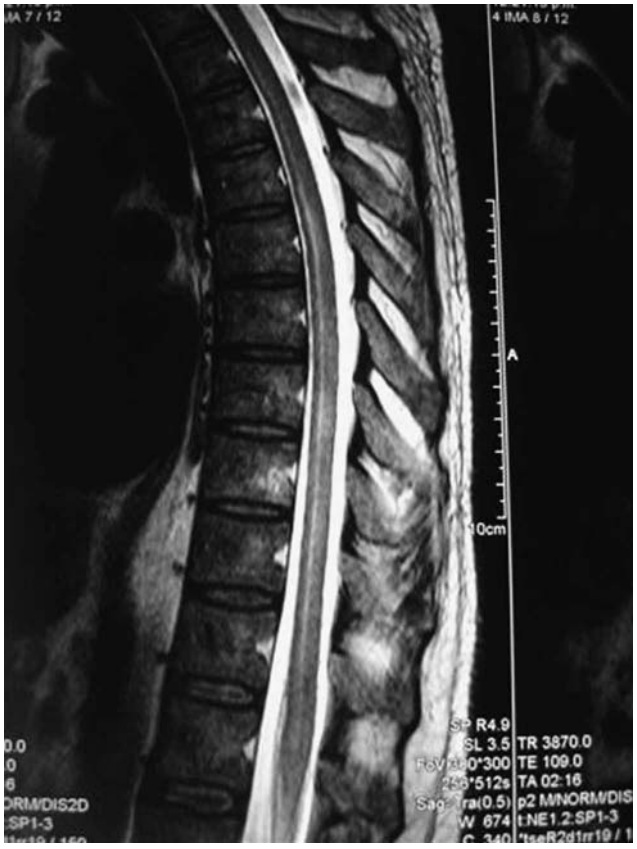

Figure 1 Sagital MR that shows the hyperintense signal from D5 to D12.

Discussion

We identified a patient with previous history of YF vaccine that presented a longitudinal myelitis and in which high titers of YF vaccine antibodies were found in CSF.

Historically, encephalitis was reported in infants younger than 7 months after administration of YF vaccine (Cetron *et al,* 2002). However, such events were markedly reduced after 1969 by restricting use of the vaccine in infants less than 6 months of age (Kitchener, 2004). In the last 15 years, new cases of neurological disease after YF vaccine have been reported. For this reason, the Centers for Disease Control and Prevention (CDC) have enhanced surveillance and created the Yellow Fever Working Group (YFWG) to control, investigate, and report the YF vaccine associated with adverse events (McMahon *et al,* 2007).

This group of specialists described three syndromes of YF-AND: postvaccinal encephalitis, ADEM, and Guillain-Barré syndrome. The assessment of causality for neurological adverse events following YF vaccine was based on the diagnostic finding of YF-specific IgM in the CSF ((McMahon *et al,* 2007). Similar adverse events were described in Europe and Brazil; however, in those final reports

there was no serological confirmation of the association (Fernandes *et al,* 2007; Lindsey *et al,* 2008).

Regarding the serological confirmation, because IgM does not normally cross the blood–brain barrier, the presence of IgM antibodies in CSF suggests intrathecal antibody production in response to a nervous system infection. A limitation to this approach is that there is no published information on YF-specific IgM in CSF in YF vaccine recipients without adverse events. Nevertheless, the YFWG considered that the presence of YF-vaccine specific IgM in CSF in the cases with clinically compatible illness and a temporal association with YF vaccination is enough evidence to conclude that the illness is caused by YF vaccine, particularly when there is neither clinical, epidemiological, nor serological evidence of concurrent infection with a different flavivirus, and when there is no apparent alternative etiology (McMahon *et al,* 2007; Lindsey *et al,* 2008). Our patient did not experience any symptoms such as fever or headache shortly after the vaccination that could provide an alternative explanation of the YF-IgM in the CSF.

Several vaccines, including smallpox, hepatitis B, influenza, rubeola, and rabies vaccines have been associated with ADEM as an adverse event following the vaccination. The wide spectrum of vaccines that appear to trigger the adverse event suggest that multiple or nonspecific immune activation (molecular mimicry or superantigens stimulation) may trigger the event in a susceptible individual (Lindsey *et al,* 2008). Despite the previous reports that described neurological adverse events, ours is the first to describe longitudinal myelitis as a serious adverse event associated with YF vaccination in which serological confirmation of the presence of antibodies in CSF was found. To date, it is also the first report with serological confirmation in Argentina and in South America.

We also observed the presence of symptoms 45 days after the vaccination being that period of time highly atypical. Previous reports point out that adverse events related to YF vaccination have a maximum time frame of 30 days. However, the passive surveillance system for adverse event following immunization (VAERS), operated collaboratively by the CDC and the U.S. Food and Drug Administration after the evaluation of all adverse events related to YF vaccine reported from 2000 to 2006, considered that the time frame that an adverse event associated with a live vaccine (including YF vaccine) is likely to occur is 60 days (Lindsey *et al,* 2008; Iskander *et al,* 2004; Varricchio *et al,* 2004). It is important to highlight this issue in order to be aware of the possibility of an adverse event related to YF vaccination even in patients in which vaccination occurred beyond 30 days.

In conclusion, YF vaccine adverse reactions were suggested to be related to elderly people, to have a clinical manifestation as Guillian-Barré syndrome, ADEM, or encephalitis, and to develop between 5 and 30 days after the vaccination. However, we describe a patient younger than 60 years who developed a different neurological manifestation (longitudinal myelitis) and began with the disorder after the period that had been previously reported in the literature.

We consider that the present investigation will raise awareness in the region in the reporting of adverse events related to YF vaccine and improve our knowledge of adverse reactions to the vaccine.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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