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Infant meningoencephalitis caused by yellow fever vaccine virus transmitted via breastmilk

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Abstract

Objective: To describe a case of infant meningoencephalitis that was probably caused by yellow fever vaccine virus transmitted via breastmilk.

Description: A 38-day old patient was admitted to hospital on May 23, 2009, with fever. On May 25, 2009, convulsive crises began. Cerebrospinal fluid (CSF) test results were suggestive of meningoencephalitis. The mother had been given a dose of yellow fever vaccine and the baby was on exclusive breastfeeding. The baby was discharged after the convulsive crises were controlled. Tests identified IgM antibodies specific for yellow fever in both serum and CSF.

Comments: In 2009, the first case was confirmed of meningoencephalitis caused by the yellow fever vaccine virus transmitted via breastmilk. We describe a second case in which the vaccine virus was possibly the etiologic agent of meningoencephalitis. The Brazilian Ministry of Health now recommends delaying vaccination of nursing mothers until their children reach 6 months or providing them with guidance on alternative options to avoid the risk of transmission of the vaccine virus via breastmilk.

J Pediatr (Rio J). 2011;87(3):269-272: Adverse events, yellow fever vaccine, encephalitis, convulsions, breastfeeding.

Introduction

Yellow fever is an acute systemic febrile disease, caused by an arbovirus (*Flavivirus*) and transmitted by infected mosquitoes. The disease is endemic in 12 states in Brazil, and epidemics occur in other regions.[1] To date there is no specific treatment.[2,3] Vaccination is the principal public health strategy to control the disease. The yellow fever vaccine was added to Brazil's Expanded Immunization Program in 1998 and is recommended from 9 months of age onwards; in endemic areas it is administered from 6 months.[1] Several mild adverse effects have been described after administration of the vaccine, such as headaches, myalgia and pain at the injection site. Severe adverse events include: anaphylactic shock, neurological diseases and viscerotropic disease; all of which are potentially

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fatal.[1-4] Deaths of primates were reported in several parts of the Brazilian state of Rio Grande do Sul between October of 2008 and July of 2009 and the cause of death of the majority of these animals was yellow fever. As a result, it was recommended that part of the state's population be vaccinated.[5] The first confirmed case of meningoencephalitis caused by the yellow fever vaccine virus and transmitted via breastmilk was confirmed in a 23-day-old infant during April of 2009.[6] We describe the second such case in the state, which was investigated during the same period.

Case description

A 38-day-old, white, male patient was admitted to hospital with fever on May 23, 2009, in the town of Cachoeirinha, state of Rio Grande do Sul. Prenatal care had been adequate and there had been no intercurrent conditions during pregnancy. Born weighing 3,070 g, by caesarean delivery, at a gestational age of 37+4 weeks and with Apgar 9/10, he was discharged with his mother, already breastfeeding exclusively. The family received a health visitor at home on April 28, 2009 and the mother was offered and accepted the yellow fever vaccine (batch 09101B0072). Approximately 24 hours before hospital admission, the baby presented with prostration and fever with no signs suggestive of location. Work-up test results were as follows: white blood cell count: 19,900, 3% band cells; platelets: 229,000; cerebrospinal fluid (CSF) with a hemorrhagic appearance and 3 cells; CSF glucose: 53 mg/dL; CSF protein: 202 mg/dL. Empirical antibiotic therapy was started with ampicillin and gentamycin. Cerebrospinal fluid culture was negative. On May 25, 2009, the infant suffered a tonic-clonic convulsive crisis of the left half of the body, which resolved spontaneously. On the following day he suffered a similar crisis, but this time needed diazepam 0.25 mg/kg/dose and inhaled oxygen. His blood glucose test result was 79 mg/dL. He was given an attack dose of phenobarbital (15 mg/kg), maintained at 5 mg/kg/day. Laboratory work-up was repeated: white blood cell count: 12,500, 3% bands. The case was notified to the Rio Grande do Sul State Health Department (SESRS) after the national press reported another baby admitted to hospital after its mother had been given the yellow fever vaccine, at the start of May 2009. A further CSF sample was taken and sent to the state's central laboratory, to test for dengue and yellow fever. This second CSF sample was clear and contained 66 cells, 1 red blood cell; CSF glucose: 34 mg/dL; CSF protein: 229 mg/dL; CSF culture: negative again. The infant continued to suffer convulsive crises and was transferred to the pediatric intensive care unit (PICU) of a hospital in the state capital the same day. On admission, the patient was in a good general state, somnolent, but with no focal signs. Treatment was changed to ampicillin and cefotaxime with phenytoin (10 mg/kg/day). No anatomic abnormalities were detected by cerebral echography. An electroencephalogram taken on June 3, 2009, showed multifocal irritant activity. The patient remained somnolent, but with no further convulsive crises. Phenytoin was withdrawn gradually. Serum phenobarbital was tested and found to be 50 mcg/mL (therapeutic concentration is 15 to 40 mcg/mL) and the dose was reduced to 4 mg/kg/day. The patient exhibited good clinical progress, tolerated reductions in the anticonvulsant dosages and phenytoin was fully withdrawn on June 2, 2009. The child was discharged on June 7, 2009, in a good general condition, active and reactive, with the convulsive crises controlled, still on phenobarbital (4 mg/kg/day) and free from motor deficits. Serum and CSF were both positive for yellow-fever-specific IgM antibodies according to tests performed at the Instituto Adolfo Lutz, in São Paulo, which is a center of laboratorial excellence belonging to the Brazilian Ministry of Health. It was not possible to test for the vaccine's RNA in CSF. Phenobarbital was withdrawn gradually with no further convulsive crises. The patient remained in outpatients follow-up with a pediatric neurologist at a hospital in the state capital. At the most recent consultation, in June 2010, the child was 1 year and 2 months old and exhibited adequate neuropsychomotor development.

Discussion

The yellow fever vaccine is made using live attenuated virus and has been available since 1937, has efficacy greater than 95% and is well-tolerated in the majority of cases.[7] In Brazil, the vaccine is manufactured by the Fundação Oswaldo Cruz, using strain 17D.[1] Approximately 3 days after vaccination, viremia can be detected and can last 5 days in the majority of individuals. The majority of adverse reactions that are described are mild, such as myalgia, fever, headaches, pain at the injection site and allergic reactions.[2] There have been several reports of potentially fatal adverse events associated with this vaccine, the majority of which occur after the first dose.[2-4,6] Neurological adverse events include meningoencephalitis (neurotropic disease, caused directly by the vaccine virus itself), acute disseminated encephalomyelitis, Guillain-Barré syndrome and bulbar palsy, which are autoimmune manifestations related to vaccination.[2]

In 2001, in the Brazilian city of Juiz de Fora, state of Minas Gerais, 12 cases of acute aseptic meningitis were reported following a mass vaccination campaign – all probably associated with the yellow fever vaccine.[8] Vaccine-related neurological problems are most common in infants less than 6 months old, and vaccination is contraindicated in this age group.[1,2,9] Immunodepressed patients are also at risk of developing post-vaccination encephalitis. A study using immunodepressed hamsters demonstrated

that the attenuated 17D yellow fever virus vaccine exhibits neurotropism, and 50% of the immunodepressed animals developed progressive encephalitis.[10] The yellow fever vaccine is contraindicated in post-transplant patients, patients with primary immunodeficiencies, malignant neoplasms or symptomatic HIV infections and for patients on immunosuppressive or immunomodulatory treatments. In all of these cases there is an increased risk of severe adverse events associated with the vaccine.[2]

In the case described in this article, the infant's symptoms began 24 days after the mother was given the yellow fever vaccine, whereas the majority of adverse events take place during the first few days after vaccination.[2] Nevertheless, the time reported between vaccination and onset of neurological symptoms, such as meningoencephalitis, Guillain-Barré syndrome and acute disseminated encephalomyelitis, varies from 3 to 28 days.[2,11] The greatest reported interval between administration of the vaccine and onset of symptoms of an adverse neurological event was 45 days, in an adult patient aged 56 who suffered myelitis.[12]

The first confirmed case of secondary meningoencephalitis due to transmission of the vaccine virus in breastmilk occurred in the South of Brazil, in April 2009.[6] Tests identified reactive IgM specific for yellow fever in serum and CSF. The presence of reactive IgM in serum could be explained by maternal IgM (produced 4-7 days after vaccination) transferred in breastmilk, but the identification of specific IgM in the baby's CSF indicates local antibody production. There is also the possibility that the baby had contracted the disease itself and that this increase in IgM was caused by wild virus and not vaccine virus. However, in the first case described in the literature, the RNA of the 17D vaccine virus was identified in CSF, which definitively confirmed the association with vaccination.[6] In the case described here it was not possible to test for viral RNA, but there had been no cases of yellow fever in human beings in the town in which the family lives during the period in question. The vaccine was offered and administered at home by health visitors because the town bordered the region where the primate deaths had occurred.[5]

On January 14, 2010, the Brazilian Ministry of Health released a technical statement on vaccination against yellow fever in breastfeeding women. The statement recommends delaying vaccination of nursing mothers until their children reach 6 months or, when vaccination cannot be delayed, providing guidance on alternative options that avoid the risk of transmission – for example expressing and freezing breastmilk before vaccination for use during the period of viremia (approximately 14 days after vaccination) or referring the mother to a human milk bank.[13] The safety of vaccinating pregnant women has not been adequately investigated.[2]

In this article we have described a case of meningoencephalitis that was probably caused by the yellow fever vaccine virus transmitted in breastmilk. Faced with a case of infant meningoencephalitis, pediatricians should be aware of this possibility and the mother's vaccination history should be considered alongside that of the baby.

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