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CASE REPORT

Nonfebrile Seizures after Mumps, Measles, Rubella, and Varicella-Zoster Virus Combination Vaccination with Detection of Measles Virus RNA in Serum, Throat, and Urine

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We report the case of a child presenting with nonfebrile seizures 6 and 13 days after the first vaccination with a measles, mumps, rubella, and varicella (MMRV) combination vaccine. Measles virus RNA was detected in the patient's serum, throat, and urine. Genotyping revealed the Schwarz vaccine virus strain.

CASE REPORT

An 11-month-old boy was presented to the pediatric unit after experiencing three seizures in the morning of the same day. The seizures were initiated by a sharp outcry with symmetric tonic-clonic movement of the arms and legs. During the seizures, the child was not reacting to his mother and had cyanotic lips. Seizures stopped spontaneously, without the administration of anticonvulsants, after approximately 1 to 2 min. Immediately after the seizures, body temperature, as measured by the mother as well as by the emergency physician, was not elevated (37.3°C). Upon admission, the child was sleepy but conscious and without signs of meningitis. The child had a slight rash on his trunk and pale skin color; otherwise, the clinical examination was unremarkable.

There was no history of seizures before or any other known medical conditions. Six days before the seizure, the first vaccination with the regular measles, mumps, rubella, and varicella (MMRV) vaccine (Priorix-Tetra; GlaxoSmithKline) was performed. In the meantime, there were no signs of infection or fever. All blood parameters on admission were unremarkable except slight leukopenia of $4.3 \times 10^3/\mu l$ (normal range, 6.0×10^3 to $17.0 \times 10^3/\mu l$). All values determined by testing the cerebrospinal fluid (CSF) taken on admission were within the range of normal (CSF protein, 221 mg/liter [normal range, 150 to 450 mg/liter]; glucose, 64 mg/dl [normal range, 50 to 75 mg/dl]; lactate, 1.4 mmol/liter [normal range, 1.2 to 2.1 mmol/liter]; leukocyte count, 2 cells/μl [normal, <4 cells/μl]; erythrocyte count, 0 cells/μl [normal, 0/μl]). CSF tested negative by PCR or reverse transcription (RT)-PCR for herpes simplex viruses 1 and 2, varicella-zoster virus, rubella virus, mumps virus, and measles virus (MeV) (Table 1). A cranial magnetic resonance scan revealed no pathological findings. In a blood sample and a throat swab taken upon admission as well as in a urine sample collected the following day, MeV RNA was detected by real-time RT-PCR by amplifying a 114-nucleotide fragment of the MeV nucleoprotein N gene.

Viral concentration was low in serum and urine but remarkably higher in the throat swab. Genotyping by amplification of a total of 507 nucleotides of the variable genomic region of the MeV nucleoprotein N gene was performed by using one nested and two heminested PCRs and revealed an MeV genotype A virus. The amplified sequence included the 450 nucleotides encoding the C-terminal 150 amino acids of the MeV nucleoprotein N; this is the minimum amount of data required for determining the MeV genotype, as recommended by the WHO (1). The MeV nucleotide sequence was identical to that of the Schwarz MeV vaccine strain (Fig. 1).

TABLE 1 Detection of measles, mumps, rubella, herpes simplex viruses 1 and 2, and varicella-zoster virus by PCR or RT-PCR in serum, throat swab, urine, and CSF

RNA or DNA[a]	Detection of RNA or DNA in clinical specimens[b]			
	Serum[c]	Throat swab[c]	Urine[d]	CSF[d]
Measles virus RNA	+; <1,000 copies/ml	+; 5.81×10^5 copies/ml	+; <1,000 copies/ml	−
Mumps virus RNA	−	−	−	−
Rubella virus RNA	−	−	−	−
Herpes simplex virus 1 and 2 DNA	−	−	−	−
Varicella-zoster virus DNA	−	−	−	−

[a] Primers and protocols are available upon request.
[b] +, detection of viral genome; −, viral genome not detected.
[c] Specimen collected 6 days postvaccination.
[d] Specimen collected 7 days postvaccination.

No IgG antibodies against measles, mumps, and rubella viruses were detectable upon admission (detection of MeV antibodies was performed by IgG and IgM enzyme-linked immunosorbent assay [ELISA; Enzygnost anti-measles virus/IgG and Enzygnost anti-measles virus/IgM; Siemens Healthcare Diagnostics, Eschborn, Germany]).

After an unremarkable hospital course, a fourth seizure episode occurred on the 13th day after the vaccination, while the child was still in the hospital. While the seizures did not fulfill all criteria of a provoked seizure due to the absence of fever, antiepileptic treatment with levetiracetam was started. The remaining

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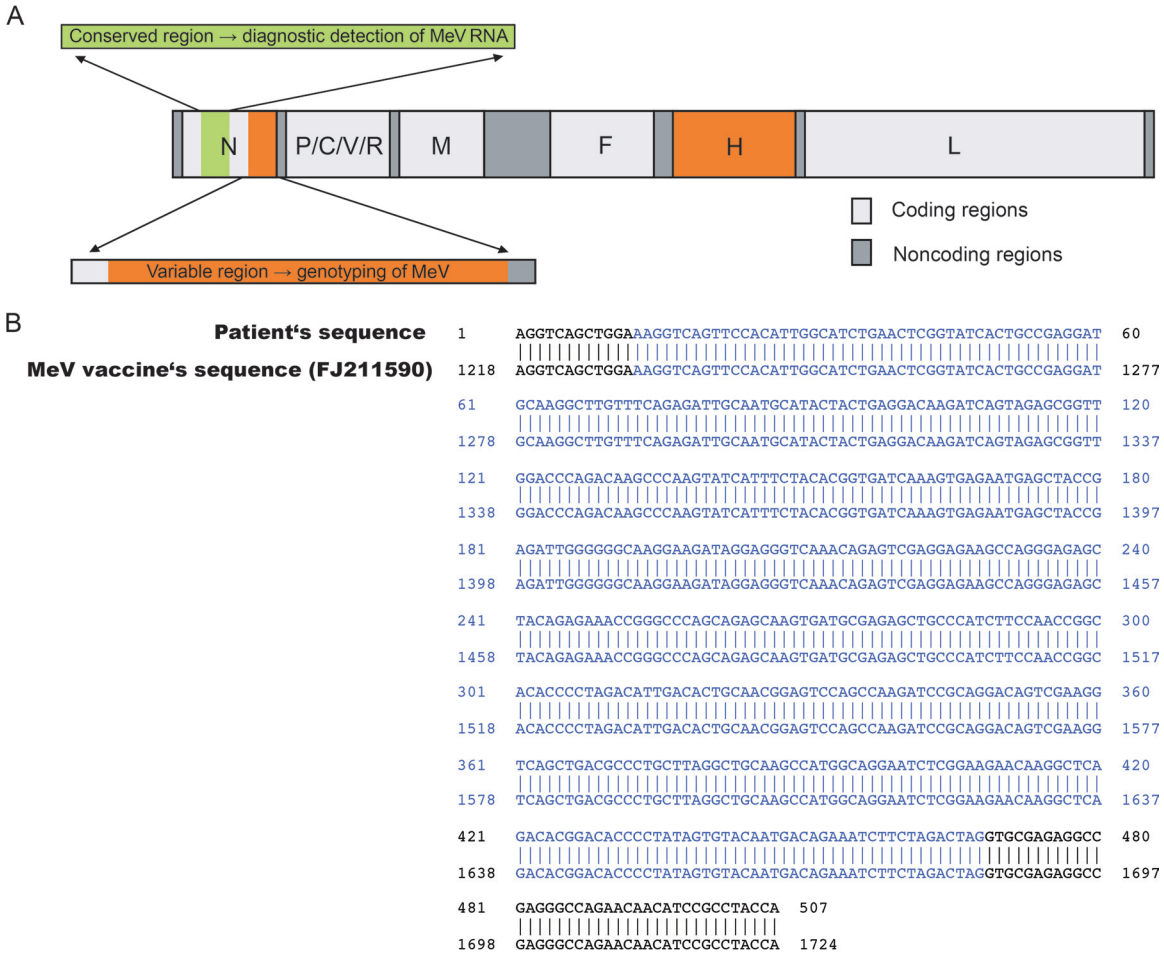

FIG 1 Strategy for identification and genotyping of the measles virus (MeV). (A) Scheme of the MeV genome. The conserved and variable regions used for MeV virus screening and genotyping, respectively, are indicated with arrows. (B) Comparison of the nucleotide sequence for the 507-bp MeV genome fragment obtained from the case patient by the genotyping RT-PCRs (upper rows) and the sequence of the Schwarz MeV vaccine strain (lower rows) (GenBank accession no. FJ211590) using the BLAST algorithm (http://www.ncbi.nlm.nih.gov/blast). Numbers before and after each row refer to the nucleotide position of the respective nucleotide sequence. The minimum requirement for MeV genotyping as defined by WHO within the sequenced genome fragment is indicated in blue.

course of hospitalization was uneventful, and the child was discharged on the 9th day of hospitalization in good health. Temperature was measured regularly during the complete course of disease and was elevated only once, up to 38.3°C, on the 3rd day of hospitalization; however, no seizure was observed in association with this episode.

Regular follow-up visits have not revealed any signs of epilepsy so far, and now, more than 1 year after the vaccination, the child remains well. The therapy with levetiracetam was continued without any side effects. In a blood sample taken 3 months after the vaccination, high antibody values against mumps, measles, and rubella viruses were found, but no antibodies against varicella-zoster virus could be detected.

MeV is one of the most contagious infectious diseases in humans and among the leading causes of death in children (2). Vaccination with live attenuated measles vaccine is the most effective measure for control and eradication (3, 4). Most vaccines used today are based on the Schwarz vaccine strain (genotype A) (5).

Fever is the most common complication of immunization and occurs most often after administration of live attenuated vaccines, toxin-containing vaccines, or whole-cell preparations (6). Adverse events after vaccination against measles, mumps, rubella, and varicella are generally mild. Besides a local reaction at the site of injection, fever, and rash, the most common neurologic adverse events are febrile seizures, commonly 7 to 10 days after vaccination (7, 8). Febrile seizures in general have a favorable outcome and are not associated with neurologic sequelae. While a higher risk for febrile seizures was observed with the MMRV combination vaccine than with the MMR vaccine (8), nonfebrile seizures in association with MMRV or MMR vaccination have not been described so far.

Therefore, a search was performed in the database of the German Federal Institute for Vaccines and Biomedicines (Paul Ehrlich Institute [PEI], Langen, Germany), which collects and evaluates the reports of adverse events, and two further cases were revealed. In the first case, a 9-year-old male experienced convulsions leading to hospitalization 14 days after he had received the second dose of MMRV (MMRVaxPro; Sanofi Pasteur MSD). His symptoms

resolved (the duration of symptoms was unspecified), and the patient was discharged after 2 days of hospitalization. The second case was an 11-month-old female who presented with a tonic-clonic seizure, allergic reaction, and exanthema 1 day after having received an unspecified dose of MMRV (Priorix-Tetra; GlaxoSmithKline) on 10 February 2011. Further seizures without fever in the same child occurred on two more occasions, two and three days after having received vaccinations on 14 March 2011 against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, hepatitis B, poliomyelitis (Infanrix hexa; GlaxoSmithKline), and *Streptococcus pneumoniae* (Synflorix; GlaxoSmithKline), without any further pathological findings noted in the hospital report. So far, it is not possible based on these cases to assess a causal relationship between nonfebrile seizures and vaccination. Further awareness is necessary to evaluate whether nonfebrile seizures temporally associated with vaccine exposure have to be considered a potential adverse effect. However, it should be stressed that all children with seizures, either febrile or nonfebrile, had a favorable outcome according to available follow-up data.

Even though live attenuated measles vaccines have been used for more than 40 years, data are scarce on the extent to which vaccine virus replicates in or is shed by vaccinees (5). Isolation of infectious vaccine virus from the blood and pharynx of vaccinated children by propagation on canine renal cell culture was successfully performed in early studies with the Edmonston strain (9), from experimentally vaccinated *Cynomolgus* monkeys after vaccination with the Schwarz vaccine strain (10), and in a study evaluating fever and rash appearing 3 to 9 days after measles vaccination (11). In this study, in 6 of 7 children, wild-type virus was isolated from peripheral blood leukocytes or throat swabs, suggesting vaccination during the incubation period of wild-type MeV. In only 1 of 7 patients, vaccine virus (strain Handai) was isolated from blood leukocytes, and this child had the mildest clinical course (mild fever without rash appearing on day 7 after vaccination) (11). It is not stated in the above-mentioned study if the children, in whom Edmonston vaccine virus isolation was achieved, presented with any symptoms or were asymptomatic (9). Further, Edmonston vaccine virus RNA was detected by RT-PCR 13 days after vaccination in the serum of an HIV-positive, 1-year-old boy who presented with measles-like illness 10 days after MMR vaccination (12).

For the Schwarz vaccine strain, there are two case reports about healthy children that describe demonstration of vaccine virus in the throat of a 3-year-old boy (13) and detection of vaccine virus RNA in the throat and urine of a 14-month-old child (14). The first child presented with fever, pharyngitis, and adenopathy 8 days after vaccination. MeV was isolated in cell culture from a throat swab taken 4 days after fever onset. The 14-month-old child in the second case report presented with facial erythema without fever 5 days after vaccination, followed by fever and rash 8 days after vaccination. MeV RNA was detected by RT-PCR from a throat swab taken 5 days and from a urine sample taken 6 days after the onset of fever. In both children, the virus RNA could be characterized as the Schwarz strain, and both children had a favorable follow-up. Taken together, the results from the three reports, including ours, show that Schwarz vaccine strain RNA is present in blood at least at day 6 postvaccination and is detectable in throat and urine at days 7 to 15 postvaccination. However, the clinical relevance of detection of vaccine virus or its RNA from the different body compartments, if any, remains unclear. To the best of our knowledge, so far there are no reports of transmission of vaccine measles virus.

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We report no conflicts of interest.

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