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Detection of measles vaccine virus and measles-specific immunoglobulin M in children vaccinated against measles-mumps-rubella during measles outbreak

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ABSTRACT

Information regarding the detection perioid of measles vaccine virus (MeVV) RNA in human nasopharyngeal samples and measles-specific antibodies following measles-mumps-rubella (MMR) vaccination is limited. During contact tracing for a measles outbreak at a hospital in Republic of Korea, 4 out of 206 children vaccinated with MMR underwent real-time RT-PCR assay for measles and measles-specific antibodies test. Measles virus RNA was detected in 2 children, all of which was vaccine virus strain RNA (genotype A). In a healthy 27-month-old boy, MeVV RNA was detected 448 days after MMR vaccination. Measles-specific IgM was positive 1097 days following vaccination in a 4-year-old girl. MeVV RNA and measles-specific IgM were detected for a considerable period following primary MMR vaccination. Physicians should exercise caution when interpreting positive RT-PCR results for MeVV or measles-specific IgM from a child with measles-associated symptoms who has been recently vaccinated against measles.

Introduction

Measles is an acute, self-limited febrile illness caused by the measles virus. The Republic of Korea (ROK) was certified by the World Health Organization as having eliminated measles in 2006 owing to the introduction of the measles vaccine and continuation of the national vaccination program. Most measles cases in the ROK at present are associated with international travel from measles endemic areas [1–3].

Based on the Korean National Immunization Program (NIP), children in the ROK receive measles vaccination at the ages 12–15 months and 4–6 years. The trivalent measles-mumps-rubella (MMR) vaccine, a measles vaccine used in Korea, is a live attenuated vaccine. Therefore, the measles virus, not just measles-specific antibodies, can be detected in the nasopharyngeal swab specimen for a period after vaccination. However, information on how long the measles vaccine virus (MeVV) in human nasopharyngeal samples will be detected after the vaccination is limited [4–6].

Most countries, including the ROK, monitor and manage measles if an outbreak occurs. In the event of an outbreak at a hospital, all exposed healthcare workers and patients are assessed for immunity against measles, and are monitored for measles-related symptoms. However, measles-specific immunoglobulin M (measles-IgM), measles-specific immunoglobulin G (measles-IgG), and MeVV RNA could be detected among children who have recently received the measles vaccine regardless of the development of measles. Therefore, the detection of MeVV RNA and measles-IgM post-vaccination presents diagnostic challenges in the setting of recent vaccination and known exposure.

We experienced an outbreak of measles, which was caused by a citizen returning from China and two people in our hospital subsequently being infected. We detected MeVV RNA and measles-IgM in

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; MMR, measles-mumps-rubella; MeV, Measles virus; RT-PCR, Real-time reverse transcriptase polymerase chain reaction; ROK, Republic of Korea.

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MMR-vaccinated children during contact tracing. Here, we report the long-period detection of MeVV RNA and measles-IgM observed during the monitoring.

Materials and methods

Case definition

A clinical case was defined as the occurrence of rash and/or fever and underwent laboratory tests. A laboratory-confirmed case was defined as a clinical case patient with one or more of the following results: the presence of measles-IgM in serum or measles viral RNA in a nasopharyngeal swab. Measles-IgM and measles viral RNA tests were performed on the same day.

Measles-IgM and IgG

Measles-IgM in serum was identified using an IgM capture enzyme immunoassay (EIA), as described previously [7]. Measles-IgG in serum was identified using an enzyme-linked immunoassay (ELISA) for measles IgG (Luebeck, Germany). The test results were interpreted following the manufacturer instructions.

Real-time reverse transcription polymerase chain reaction for measles virus detection

Nasopharyngeal swabs were sent to public health laboratories for real-time reverse transcription polymerase chain reaction (RT-PCR). A real-time RT-PCR assay was performed to detect the measles virus N gene using the 7500 Fast Real-time RT-PCR system (Applied Biosystems). The amplification used forward (MVN1139-F:5′-TGGCATCT-GAACTCGGTATCA C-3′) and reverse (MVN1213-R:5′-TGTCCTCAGTAGTATGCATTGCAA-3′) primers. A probe (MVNP1163-P:5′-CCGAGGATGCAAGGCTTGTTTCAGA-3′) was labelled at the 5′ terminus with a fluorescent reporter dye and 6-carboxyfluorescein; and at the 3′ terminus with a non-fluorescent quencher and black hole quencher-1. Real-time RT-PCR assays were verified and used by the Standard Operation Protocol Verification Committee of the Korea Disease Control and Prevention Agency.

Genotype identification and genetic analysis

Viral RNA was extracted from nasopharyngeal swab samples using a QIAamp Viral RNA Mini Kit (Qiagen, Venlo, Netherlands), following the manufacturer instructions. The highly variable 450-nucleotide (nt) region in the carboxy-terminus of the nucleocapsid protein (N-450) was amplified and sequenced for genotyping using forward (MeV216:5′-TGGAGCTATGCCATGGGAGT-3′) and reverse (MeV214:5′-TAA-CAATGATGGAGGGTAGG-3′) primers. RT-PCR was performed using the OneStep RT-PCR Kit (Qiagen, Venlo, Netherlands), following with the manufacturer instructions.

This study was approved by the Institutional Review Board of our hospital with a waiver of informed consent due to the study being retrospective and demploying de-identified data collection (IRB No. 2022–06-014).

Results

Index case** and **contact tracing

The index patient in our contact tracing for measles was a 41-year-old man who returned from China. He visited our hospital with a fever, cough, and rash in May 2018. Conjunctival and pharyngeal injection and maculopapular rashes were observed on physical examination. He was diagnosed with measles by RT-PCR with a measles virus genotype of D8, which circulates in China. A total of 803 individuals, including 206 children, were exposed to the index case and two subsequent cases infected by the index case. They were all monitored by our hospital's infection control team for 21 days after exposure. The median age of the children was 4.0 years (interquartile range [IQR], 2.1–8.3 years), and their age distribution was as follows: age < 1 year, n = 17 (8 %); 1 to 4 years, n = 83 (40 %); 4 to 12 years, n = 80 (39 %); 13 to 18 years, n = 26 (13 %). There were 86 girls and 120 boys.

Four children tested for measles RT-PCR during the monitoring

Of the 206 children, 4 developed rash and/or fever. The first child was a healthy 27-month-old boy. He developed cough and rhinorrhea 10 days after exposure and exhibited conjunctival injection the next day without fever. He had wheal-like skin lesions on his face and torso and came to the hospital 13 days after exposure. He had no Koplik spots. His siblings had upper respiratory tract infection and conjunctivitis. He was thought to be infected by his siblings. However, he was positive on RT-PCR testing for measles, and the genotype was A (the vaccine strain).

The second child was a healthy 18-month-old girl attending daycare. On the fifth day after exposure, she presented with cough, sputum production, rhinorrhea, and fever. She had multiple maculopapular rashes on both extremities. She visited the hospital six days after exposure and had no conjunctival injection or Koplik spots. Her measles RT-PCR result was positive for genotype A.

The third child was a healthy 19-month-old girl. She visited our hospital because of a fever that occurred on the day and was exposed to measles at then. The fever resolved three days later, and multiple macular rashes appeared. She visited our hospital on the seventh day after exposure and was clinically suspected of having roseola. However, the patient underwent RT-PCR testing for measles due to a history of exposure. The result was negative.

The fourth child was a 4-year-old girl with a medical history of acute meningoencephalitis treated a couple of weeks ago. She had received her first dose of MMR vaccine at 12 months of age and had not yet received a second dose of MMR vaccine. She came to our hospital with a fever that started one day prior and was exposed to measles then. The fever resolved two days later-on the second day after exposure- and macular rashes developed. The next day, the rashes disappeared; on the same day, measles RT-PCR was performed on the third day after the exposure. The result was negative.

All four children experienced improved symptoms with only conservative treatment. Although they fit laboratory-confirmed cases, we did not diagnose them with measles given various factors.

Measles vaccine virus in the nasopharynx and measles-IgM in serum

We confirmed that the four children with rashes had received MMR vaccination through the NIP records (Table 1). The vaccines included M-M-R II (Merck Sharp & Dohme Corp., West Point, Pennsylvania, US) and

Table 1
Details of cases tested for measles RT-PCR.

Case	Age, Sex	Measles RT-PCR	Days of post-vaccination on day of measles testing	Vaccine	Measles IgM/IgG
1	27 m, M	positive (Genotype A)	448	Priorix	Borderline/+
2	18 m, F	positive (Genotype A)	208	M-M-R II	+/+
3	19 m, F	negative	234	Priorix	N/A
4	4y, F	negative	1097	Priorix	+/Borderline

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; N/A, not available; RT-PCR, reverse transcriptase polymerase chain reaction.

Priorix (GSK Biologicals, Rixensart, Belgium). They all received the first dose of measles vaccination between 12 and 15 months according to Korea's recommended vaccination schedule.

The measles viral RNA detected from the two children was the vaccine virus strain. The MeVV RNA was detected 448 days after vaccination in a 27-month-old boy (first child), and up to approximately 7 months after vaccination in an 18-month-old girl (second child).

Three children were tested for measles-specific antibodies; The other (third child) was not tested due to parental refusal. In the 4-year-old girl (fourth child) with negative measles RT-PCR, measles IgM, which was performed approximately three years after the first vaccination, was positive. Her measles-IgG was borderline. In the 18-month-old girl, both measles-IgM and IgG were positive on the 208th day after vaccination (second child). The results for the measles-IgM and IgG of the first child were borderline and positive, respectively.

Discussion

In this report regarding a measles outbreak in our hospital, we identified MeVV RNA in nasopharyngeal specimens up to 448 days after the first dose of MMR vaccination. Furthermore, measles-IgM was positive at 1097 days after vaccination.

The MeVV was detected up to approximately 15 months after vaccination in a 27-month-old boy in our outbreak. Although MeVV detection in human nasopharyngeal samples after vaccination is biologically possible, few reports are available on its long-period detection. One study by Murti et al. reported that the measles vaccine virus was detected in the nasopharynx five weeks post-vaccination [4]. McMahon et al. reported that the measles vaccine virus was detected in children vaccinated with measles up to 548 days after the first MMR vaccination and up to 471 days after the second dose of MMR [5], and the majority of individuals detected with MeVV were children between the ages 1–4 years [6]. The long-period detection of MeVV may be due to the improved sensitivity of the PCR test. This long-period detection can be problematic when a person who has received the measles vaccine has a fever and/or rash.

According to a study by Helfand et al. using an IgM capture EIA method, most measles-IgM disappears by 8 weeks and less than 10 % of children remain measles-IgM positive for an additional 1 to 2 months [8]. In another study using a different detection method, measles-IgM was shown to be positive 6 months after the first dose of MMR vaccination [9]. In our case, measles-IgM was positive in two children and borderline in one child over three years following vaccination. Such measles-IgM positive results may be accurate. However, false-positive results may also exist. It has been demonstrated that the presence of IgM for other viruses, such as HHV-6, rubella, or parvovirus B19, could produce false-positive results in a measles-IgM test [9–15]. The long-term detection observed in our study, especially in the third child whose clinical diagnosis was roseola, can be the possibility of cross-reactivity. Therefore, the measles viral RNA and genotype test is crucial in diagnosing measles in vaccinated people.

We concluded that the cause of the rash in the four measles clinical cases was not measles, but other viral illnesses that can cause rashes. The order of symptom onset and physical examination findings did not support the diagnosis of measles. The likelihood of being infected with other viruses circulating then was high, considering the presence of family members with similar symptoms or attending daycare. Although the MeVV was detected in the nasopharynx, the interval between vaccination and symptom onset was long, thus the likelihood of vaccine-related measles was minimal. In the post-vaccine era, diagnosing measles requires the laboratory tests mentioned earlier and thorough history-taking. Additionally, in patients highly suspected of having measles, a measles-IgG avidity test and measles neutralizing antibody assay could be helpful [16].

These findings are based on our experiences, and this work had certain limitations. The data involved only four children with measles-related symptoms. The results involving few symptomatic children are insufficient to determine how long PCR positivity for measles lasts. It was insufficient to determine whether the detection of measles-IgM was a true or false-positive since results for other factors that could affect measles-IgM results were unavailable. Repeated checking of MeVV RNA and measles-IgM in asymptomatic individuals after vaccination may help clarify these.

Our report showed that MeVV RNA and measles-IgM were detected for a considerable period following primary MMR vaccination althogh measles-IgM results may be false-positives. These findings will help physicians interpret RT-PCR results for the MeVV or measles-IgM test results from a child with measles-associated symptoms who have been recently vaccinated against measles in conjunction with clinical and epidemiologic information.

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CRediT authorship contribution statement

Euri Seo: Data curation, Writing – original draft. **Yun-Jung Chang:** Data curation, Investigation. **Jae Woo Chung:** Formal analysis, Methodology. **Yoon-Seok Chung:** Data curation, Investigation, Methodology. **Seong Yeon Park:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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