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Conference report

Symposium report of the 19th annual meeting of the Japanese Society for Vaccinology 2015

What is the role of clinicians in vaccinology?

Dr. Toshiaki Ihara passed away on February 19, 2016. We are deeply saddened that he is not with us to summarize these proceedings because it was his desire to organize this important symposium. Dr. Ihara was a leader in vaccinology and pediatric infectious diseases in Japan. He sought to improve the vaccine gap in our country, and was an avid supporter of young investigators. His longtime colleagues at the Mie National Hospital, as well as many collaborators in the vaccinology field, collectively mourn his passing.

This inaugural symposium was organized to allow physicians and scientists an opportunity to discuss their roles in vaccinology in Japan. Currently, there was a 'vaccine gap' between Japan and the various countries such as United States, Canada, Australia, and European countries; however, this disparity has been bridged introducing new vaccines in Japan, including the vaccines developed abroad [1,2]. Preparation for the introduction of a new vaccine requires many efforts such as studies to evaluate the efficacy and safety profiles of the candidate vaccine. Moreover, it is necessary to determine whether the candidate vaccine should be introduced in our county based on clinical epidemiological studies and cost benefit analysis. After introducing a new vaccine, it is critical to conduct post-marketing surveillance and to monitor the epidemiology of the associated infectious disease. Thus, in order to expand vaccinology in Japan, it is essential to convene a meeting of key stakeholders including physicians and scientists.

1. Diagnosis of mumps and varicella among patients with vaccination history in private clinics

1.1. Introduction

In Japan, universal immunization with the varicella vaccine was introduced in October 2014. However, the mumps vaccine is voluntary. As the number of local governments that subsidize the mumps vaccine has grown, a gradual increase in the mumps vaccination rate was reported. Therefore, there was a recent upswing in the number of patients who were diagnosed as mumps with previous vaccination history. Additionally, mumps must be differentiated from parotitis related to other etiological factors that are difficult to diagnose based on clinical findings. Meanwhile, it is well known that breakthrough varicella (BV) occurs approximately 30% of the patients with one dose of varicella vaccination, which is difficult to diagnose precisely. Thus, diagnosis of these two common viral infections is major problem in private pediatric clinic. Therefore, two clinical studies were conducted to establish reliable laboratory methods for the diagnosis of mumps and varicella in private clinics.

1.2. Diagnosis of mumps virus infection

In 678 children with parotitis, we investigated the reliability of serological assays compared to virus isolation and reverse transcriptase-loop-mediated isothermal amplification (RT-LAMP) assays from saliva as golden standards. Mumps virus was isolated from 350 of the 678 throat swab samples. The RT-LAMP assay detected the mumps viral genome in 352 of the 678 throat swab samples. The numbers of unvaccinated and vaccinated (received at least one vaccine) children that expressed mumps-specific IgM antibodies were 252/289 (87.2%) and 7/67 (10.4%), respectively. Therefore, the presence of mumps-specific IgM antibodies may be unreliable for diagnosis of children with history of mumps vaccine. To determine whether or not it is possible to make a diagnosis based on acute mumps–specific IgG antibody titers in children with a history of vaccination, we conducted a receiver operating characteristic (ROC) analysis of IgG enzyme immunoassay (EIA) titers. The area under the ROC curve (AUC) was 0.83. A mumps-specific IgG antibody titer of 10 EIA was established as the cut-off value to definitively differentiate between a mumps diagnosis and parotitis without mumps infection. The sensitivity and specificity were 76.1 and 75.9%, respectively, suggesting that the diagnostic reliability of IgG antibody titers is insufficient in children with a history of vaccination. These data highlight the requirement for virological tests, such as virus isolation and RT-LAMP, to diagnosis mumps in children with a history of vaccination. In particular, the RT-LAMP method may be most useful due to its rapidity and simplicity.

1.3. Diagnosis of breakthrough varicella

Thirty-four children were suspected of having BV based on varicella-like skin eruptions that occurred more than 42 days after receiving the varicella vaccination. In order to elucidate a reliable method for the diagnosis of BV, we conducted several virological analyses, such as the detection of viral DNA in saliva or whole blood samples and detection of viral antigens in swab samples collected from skin eruptions. If VZV-DNA was detected in the skin lesions, we defined the patient as virologically diagnosed varicella. Among the 34 suspected cases, 24 children were diagnosed with BV. Among the 10 children without BV, HSV-1-DNA was detected in skin lesions from five children. In the remaining five children, varicella was denied in one child based on the serological analysis. Among the children with BV, VZV-DNA was detected in acute-phase saliva and whole blood by real-time PCR in 83.3% (20/24) and 63.6% (14/22), respectively. These data suggest that the collection of saliva, which is minimally invasive, may be replaced with

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the collection of skin lesion specimens for the virological diagnosis of BV.

In order to detect viral antigens in skin swab samples using the direct fluorescence antibody (DFA) method, the dull-edge of a scalpel was used to scrape the skin lesion. The proportion of VZV-antigen–positive children was 91.7% (22/24). In the acute phase of the disease, no patients were positive for varicella-specific IgM antibody. Meanwhile, in the convalescence phase, 65.0% (13/20) of the children were positive. Furthermore, 75.0% (15/20) of children showed a 4-fold or greater increase in their varicella-specific IgG antibody titers from the acute to convalescence phases. The AUC for the acute-phase IgG EIA titer was 0.92. The cut-off IgG antibody titer for differentiating between the children with and without BV was 20 EIA. The sensitivity and specificity of the cut off level were 86.4% and 100%, respectively. In conclusion, serologically, an acute-phase IgG antibody titer of 20 EIA or higher may be useful for diagnosis of BV. If an adequate specimen was obtained, the DFA method is also a simple and effective method for the diagnosis of BV.

2. Feedback for researchers from hospital pediatricians: important evidence from patients

2.1. Introduction

Hospital pediatricians can contribute to the development of vaccines by treating patients as well as by performing clinical studies. In the field of pediatric infectious diseases, it is important to examine the causative agent while managing the patient. In particular, hospital pediatricians attempt to identify pathogens in pediatric patients who are admitted to the hospital so that we can chose the appropriate treatments. To date, we have confirmed the causative pathogens as well as the prevalence and clinical features of vaccine-preventable diseases, including measles, varicella, mumps, rotavirus gastroenteritis, influenza, pertussis, invasive *Haemophilus influenzae* type B (Hib) infections, and invasive pneumococcal infections, based on the isolation of pathogens, gene analysis, and the measurement of paired serum antibody titers. When microbial isolates are available, the drug susceptibility profile is examined.

2.2. Clinical studies for the evaluation of vaccine efficacy and safety

In our vaccination clinic, we have measured serum antibody titers before and after vaccination with live vaccines (such as those for measles, rubella, varicella, and mumps) and have studied the adverse reactions in response to vaccination from approximately 30 years ago. We have also administered additional vaccinations to pediatric patients with primary vaccine failure (PVF) based on serological analysis. Additionally, we have conducted several clinical studies to refine the vaccination strategy in our country. The usefulness of the phase 3 and 4 measles-rubella (MR) vaccination program was demonstrated by our previous clinical studies [3,4]. Moreover, the immune response elicited by phase 2 MR vaccination was less robust than expected [5].

In order to elucidate the dose dependency of varicella vaccine for the induction of immune responses, we administered the current varicella vaccine at a reduced dose of 0.1 mL, which was 1/5 of the standard vaccination dose. Subjects that were inoculated with 0.1 mL of the vaccine showed a low immune adherence hemagglutination (IAHA) antibody seroconversion rate of 25%, suggesting that the standard virus titer of 0.5 ml is necessary to maintain the immunogenicity of the varicella vaccine [6]. A study of the effect of booster vaccination at three to five years after the initial varicella vaccination revealed a significant decrease in the IAHA antibody titers over time after the initial vaccination before the booster vaccination in 50% of the patients, and negative conversion was observed in 38% of the patients. In contrast, the antibody positive rate was 100% after the booster vaccination, and the mean antibody titer also showed a significant increase, demonstrating the utility of a two-dose vaccination schedule [7]. In addition to varicella vaccine, we also investigated the immunogenicity and safety of a two-dose mumps vaccination schedule, and the usefulness of the schedule was reported at the 18th annual meeting of the Japanese Society for Vaccinology (Fukuoka, 2014).

2.3. Encouraging young physicians

Although hospital pediatricians have a busy daily practice, they should consistently make every effort to identify causative pathogens using diagnostic laboratory methods. Such efforts will lead to more careful management of patients and a deeper understanding of infectious diseases. Moreover, they may need to consider the needs and challenges related to vaccines, which will in turn increase their motivation to engage in relevant clinical studies. Instilling these practical attitudes in the minds of young physicians can help foster their development into good clinicians. We believe that the evidence that is obtained through patient examinations has an essential role in the research and development of vaccines. In fact, hospital pediatricians can contribute essential information to the vaccine development process by transmitting important evidence obtained from patients to basic science researchers.

3. Role of University in Vaccinology

3.1. Introduction

Although ‘vaccine gap’ between Japan and the United States or Europe is decreasing, but scientific evidence for vaccine efficacy and safety remains to be insufficient in our country. The lack of precise information about a vaccine may limit our understanding of the vaccine, which may in turn negatively impact the vaccination rate. Therefore, information for vaccine efficacy and its safety based on the scientific analysis should be conducted by Japanese researchers and disseminated to the general public. The clinical laboratory at the university can facilitate data collection to ensure that there is sufficient scientific evidence to assess vaccine efficacy and safety. Additionally, the development of new methods for microbiological analysis such as real-time polymerase chain analysis (PCR) and LAMP is also performed by the clinical laboratory at universities.

3.2. Establishment of scientific evidence for vaccine efficacy and safety

In order to introduce universal immunization using the varicella vaccine, and rapidly increase vaccine coverage in Japan, initial doses of the varicella and MR vaccines were co-administered to children. Immune responses and adverse events were evaluated in 82 subjects following co-administration of varicella and MR vaccines at one year of age versus 43 subjects that received the varicella vaccine alone and 51 subjects that received the MR vaccine alone [8]. No statistical differences were detected in the immune responses against VZV, measles virus, and rubella virus or adverse events between the two groups. These findings suggested that co-administration of the varicella and MR vaccines are safe and efficacious in Japanese children.

In order to elucidate an appropriate interval between the first and second doses of the varicella vaccine, immune responses against VZV were examined at three distinct time points: 3, 6, and 12 months. The IAHA antibody titers were below the level of detection for most of the serum samples collected at the time of