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A nationwide survey of common viral infections in childhood among patients with primary immunodeficiency diseases

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KEYWORDS

Primary immunodeficiency diseases;
Respiratory syncytial virus;
Rotavirus;
Varicella-zoster virus;
Influenza virus;
Cellular immunodeficiency

Summary Objectives: Patients with primary immunodeficiency diseases (PID) are highly susceptible to various microorganisms. However, no population-based studies have been performed among common viral pathogens, such as respiratory syncytial virus (RSV), rotavirus (RV), varicella-zoster virus (VZV) and influenza virus (IV). The objective of this study was to reveal the clinical burden of these four infections among PID patients in Japan.

Methods: We conducted a nationwide survey by sending questionnaires to 898 hospitals with pediatric departments throughout Japan.

Results: Nine hundred ten PID patients from 621 hospitals were registered (response rate: 69.2%). Fifty-four of the patients were hospitalized due to these viral infections. The durations of hospitalization due to RSV and RV infections differed significantly in the PID patients with and without cellular immunodeficiency (12.0 vs 6.5 days, $p = 0.041$; and 14.0 vs 6.0 days, $p = 0.031$, respectively). There was no significant difference in the duration of hospitalization in PID patients with and without cellular immunodeficiency who were hospitalized with IV infections (7.3 vs 6.1 days, $p = 0.53$).

Conclusions: Special attention should be paid to PID patients with compromised cellular immunity who present with RSV and RV infection due to their high risk for severe disease.

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Introduction

The primary immunodeficiency diseases (PID) are a heterogeneous group of inherited disorders that may involve one or multiple components of the immune system.¹ In most PID patients, the immune response is insufficient to eliminate specific pathogens, which leads to increased rates of morbidity and mortality due to infections caused by various pathogens, including viral pathogens that are common in childhood, such as respiratory syncytial virus (RSV), rotavirus (RV), varicella-zoster virus (VZV) and influenza virus (IV). While the infectious diseases caused by these viruses are usually self-limited in healthy children, they can be fatal in immunocompromised children. In the present study, we focus on these four viruses because the infections can be rapidly diagnosed using antigen detection kits or based on the typical clinical findings in patients with VZV infection.

RSV is one of the most common pathogens of lower respiratory tract infections (LRTIs) in childhood, and is considered to be highly pathogenic in PID patients. In 2013, new indications for the use of palivizumab in children with immunocompromised conditions and Down's syndrome were approved in Japan.² It is recommended that PID patients of ≤ 24 months of age, predominantly those with T-cell dysfunctions (e.g., severe combined immunodeficiency [SCID], DiGeorge syndrome, Wiskott–Aldrich syndrome and ataxia telangiectasia), receive palivizumab to prevent severe RSV infection. In 2014, the American Academy of Pediatrics (AAP) also updated the guidance for palivizumab prophylaxis and noted that the prophylactic administration of palivizumab might be considered for immunocompromised children of less than 24 months of age during the RSV season.³ However, these recommendations were based on the results of several clinical studies that were performed in a single center.^{4–10}

Similarly, the reports on RV, VZV and IV infection among PID patients are limited.^{11–15} Although specific treatments and effective vaccines have been developed for VZV and IV in children with cancer, their efficacy has not been established in patients with PID.^{16–18} Moreover, the vaccines

against RV and VZV are live attenuated and have the potential to cause vaccine-related diseases in PID patients.^{19–22} To date, no population-based studies have been performed to clarify the incidence and actual severity of these viral infections in PID patients.

The objective of the present study was to clarify the incidence and severity of the common viral infections caused by RSV, RV, VZV and IV in PID children.

Materials and methods

Study design

The present nationwide retrospective survey was conducted to investigate the severity of RSV, RV, VZV and IV infections among children with PID. Questionnaires were sent to hospitals with pediatric departments throughout Japan. The hospitals in the survey were selected in a similar manner to that which was used in our previous study in 2008, which was performed in accordance with The Nationwide Epidemiological Survey Manual for Patients with Intractable Diseases (2nd edition 2006, Ministry of Health, Labor, and Welfare of Japan).^{23,24} We previously found that more than 90% of pediatric PID patients received regular medical care in the hospitals with ≥ 300 beds.²³ Thus, in the present study, we sent the first questionnaire to all of the university hospitals, pediatric training hospitals and hospitals with ≥ 300 beds. The present study was approved by the Institutional Review Board of Kyushu University (No. 24–145).

Delivery of the first questionnaire

The first questionnaire was delivered to inquire about the total number of patients, the disease names (based on the PID classification of the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency)¹ and the number of PID patients hospitalized for one of four viral infections (RSV, RV, VZV and IV) between January 2002 and December 2011. PID patients who were

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