Severity of Measles among Patients with Incidental Postexposure Vaccination

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SUMMARY: It has not been well elucidated whether patients with measles who have undergone postexposure prophylaxis (PEP) exhibit milder clinical symptoms than would be expected in the absence of PEP. In the present study, we compared the severity of measles of patients who had undergone incidental PEP to those of patients who had not received such prophylaxis. An outbreak of measles occurred among the personnel of the Japan Self-Defense Forces (SDF) between 7 May and 14 June 2007 at 3 camps in or near Sendai City. All patients were admitted to SDF Sendai Hospital for isolation and care. Measles was confirmed in 21 patients (age: 21.9 ± 5.9 years). Of the 15 ill recruits (persons who had just joined SDF), 8 underwent incidental PEP on 10 May, 3 days after the onset of the prodromal symptoms in the first patient. The vaccination was not originally intended as PEP and was administered within the framework of a routine vaccination program. Compared to recruits without PEP (n = 7), the admission period was 5.6 days shorter, the period with high fever (39°C or more) was 2.7 days shorter, and the maximum body temperature was 1.1°C lower in the recruits with PEP (n = 8). These results suggest that PEP ameliorates the clinical symptoms of measles.

The measles vaccine may be protective when it is administered to susceptible people after exposure, particularly within 72 h; however, its preventive effects have not been confirmed. To date, it has not been elucidated whether postexposure prophylaxis (PEP) mitigates the clinical symptoms of measles. It has been suggested that the clinical symptoms of measles in children who have undergone PEP are milder than those in children who have not (1); on the other hand, it has also been reported (2) that the clinical symptoms in children who had undergone PEP were of the same degree as those in children with natural diseases.

The Japan Self-Defense Forces (SDF) personnel in 3 camps in or near Sendai City were evacuated to the SDF Sendai Hospital as possible measles patients between 7 May and 14 June 2007 (Figure 1). All patients with measles and those suspected of having measles were admitted to the SDF Sendai Hospital for care and isolation. Measles was confirmed in 21 patients. Of these, 8 recruits (persons who had just joined SDF) had undergone measles vaccination on 10 May at Camp F, i.e., 3 days after the onset of prodromal symptoms in the first patient at that camp. Thus, although vaccination was not originally intended as PEP, it simulated PEP. In the present study, the severity of the clinical symptoms of measles was compared between patients who had incidentally undergone PEP and those who had not.

A laboratory-confirmed measles case was defined by a positive anti-measles-immunoglobulin M (IgM) titer or a 4-fold or higher increase in the anti-measles-IgG titer from acute- and convalescent-phase blood specimens that were collected 10-14 days apart. If a patient had undergone vaccination for measles within 12 weeks of the onset of symptoms, the criteria for clinically confirmed cases were used to diagnose measles, because in such cases laboratory confirmation was not applicable (3). A clinically confirmed case was defined by the presence of a generalized rash for 3 or more days, a temperature of at least 38.3°C, epidemiological linkage with another probable or confirmed case, and at least one of the following: cough, coryza, or conjunctivitis. Criteria for admission were being in a febrile state as a hospital outpatient who had had possible contact with measles patients, and the discharge criterion was the passage of 72 h after the patient had become afebrile. The prodrome was defined as the initial symptoms of measles observed prior to the appearance of the rash.

Some young non-recruits (persons who belonged to SDF more than 1 year) had also undergone measles vaccination within the framework of the measles vaccination program of the Ground SDF, which started in 2004. In Japan, the prevalence of immunity for measles is low among young adults including recruits. Thus, non-recruits, who tend to be older than recruits, are more likely to have complete or partial immunity than are recruits. This difference might affect the severity of clinical symptoms in different patients. Thus, pa-

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Patients in this study with confirmed measles were categorized as follows: recruits without PEP, recruits with incidental PEP, and non-recruits without PEP. The severity of measles was assessed by the duration of both admission and high fever (39°C or more), and by the maximum body temperature; these parameters were compared between the 3 groups. Descriptive data were expressed as the mean ± SD. The proportions of any 2 groups were compared by $\chi^2$ test. Differences between the mean values of the 3 groups were examined using one-way analysis of variance (ANOVA). When the 3-group comparison indicated significant group differences, pairwise testing with a post hoc multiple comparison procedure (unpaired t test) was carried out. Statistical analysis was performed using Stat View version 5.0 (SAS Institute Inc., Cary, Ill., USA).

The epidemic curve of the measles outbreak is shown in Figure 1. A total of 21 patients in whom measles was confirmed were admitted to SDF Sendai Hospital (Figure 1). All of the patients ($n = 21$) were males with a mean age of 21.9 ± 5.9 years (range, 18 -44 years). Of these 21 patients, 9 (43%) had laboratory-confirmed measles and 12 (57%) had clinically confirmed measles. The mean duration from the onset of prodromal signs to the onset of the rash was 3.3 ± 3.1 days (range, 0 -13 days); the mean duration from admission to discharge was 9.7 ± 5.3 days (range, 3 -23 days); and the mean maximum temperature was 39.6 ± 0.9°C (range, 38.4 -41.0°C).

Of the 21 patients, 15 were from Camp F, 4 from Camp T, and 2 from Camp S. The number of recruits from each camp were 13, 2, and 0, respectively. Thus, a total of 15 (71%) of 21 patients were recruits. The hemagglutination inhibition (HI) test carried out in April 2007 was negative for all recruits designated as patients. The measles vaccination was not performed at Camp T or Camp S before or during the outbreak. On 10 May 2007, 8 recruits at Camp F (38%) had undergone vaccination based on their negative measles antibody titers. Since the first patient at Camp F exhibited prodromal symptoms on 7 May 2007, the vaccination on 10 May simulated timely PEP (incidental PEP). The HI test for anti-measles antibody conducted in April 2007 yielded negative results for all 15 recruits. All 8 of the recruits who had undergone incidental PEP showed positive IgM enzyme immunoassay (EIA) values that were measured after the onset of clinical symptoms.

All (100%) of the 113 recruits at Camp F had undergone a measles antibody test in April, and 61 (54%) were negative. Of the 61 seronegative recruits, 54 (89%) underwent a measles vaccination on 10 May 2007, and of these 54, 8 (15%) contracted measles. At the beginning of the outbreak, the 113 recruits were residing in 12 rooms in a barrack at Camp F. Furthermore, 7 of the 61 seronegative recruits (11%) had not been vaccinated due to their clinical symptoms on 10 May 2007; 5 of these recruits had already contracted measles. The first 5 affected recruits at Camp F, who had been residing in 5 different rooms, became symptomatic between 7 May and 10 May (Figure 1). We were unable to identify either an internal or external common source (i.e., an index case).

The clinical symptoms of the recruits without incidental PEP (those who had not undergone vaccination) ($n = 7$) were more severe than those of recruits who had undergone incidental PEP ($n = 8$) (Table 1). The admission period was 5.6 days longer, the period of high fever (39.0°C or more) was 2.7 days longer, and the maximum body temperature was 1.1°C higher in the former group (without PEP) than in the latter group. Conjunctivitis was more prevalent among the recruits without PEP than among those with incidental PEP. The maximum lactate dehydrogenase (LDH) values were somewhat higher in the former group (without PEP) than in the latter group. The prevalence rates in the 2 groups were similar of each of the following: cough, rhinorrhea, headache, sore throat, diarrhea, and Koplik spots. The symptoms of non-recruits were milder than those of recruits without PEP, although the symptoms of non-recruits were comparable to those of recruits with PEP (Table 1).

Two male recruits from Camp F were suspected of having measles; these 2 recruits had undergone incidental PEP on 10 May. Although these recruits presented with a typical generalized rash and other clinical symptoms of measles, they did not satisfy the criteria for confirmed measles in terms of

| Table 1. Comparison of the symptoms of patients with measles who underwent measles vaccination just after exposure to measles patients and those of non-vaccinated patients |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Recruits without PEP ($n = 7$) | Recruits with PEP ($n = 8$) | Non-recruits without PEP ($n = 6$) | $P$ values |
| age | 20.3 ± 2.6 | 19.1 ± 2.0 | 27.3 ± 8.7 | NS |
| first case (%), | 86 | 0 | 0 | <0.0001 |
| duration of prodrome, days | 3.3 ± 4.5 | 4.0 ± 2.8 | 2.5 ± 1.5 | NS |
| duration of admission, days | 13.9 ± 5.8 | 8.3 ± 4.0 | 6.7 ± 3.2 | 0.0276 |
| duration of high fever (39.0°C or more), days | 6.7 ± 4.4 | 4.0 ± 3.2 | 3.5 ± 2.4 | 0.0568 |
| maximum temperature | 40.4 ± 0.6 | 39.3 ± 0.9 | 39.3 ± 0.6 | 0.0115 |
| cough, % | 86 | 100 | 67 | NS |
| conjunctivitis, % | 100 | 38 | 33 | 0.0104 |
| rhinorrhea, % | 71 | 75 | 0 | NS |
| headache, % | 57 | 75 | 50 | NS |
| sore throat, % | 100 | 100 | 100 | NS |
| diarrhea, % | 29 | 25 | 33 | NS |
| Koplik spots, % | 57 | 63 | 83 | NS |
| maximum LDH, IU/L | 396 ± 179 | 263 ± 61 | 332 ± 170 | 0.0860 |

1\$: The patients observed in the first wave of outbreak in SDF camp.
2\$: From onset of prodromal signs to onset of skin rash.

Mean ± SD. $P$ values represent the significance of the statistical difference of the values or proportions between recruits without PEP and recruits with PEP.

PEP, post-exposure prophylaxis; NS, not significant.
their maximum body temperature (<38.3°C). In the analysis in which these suspected patients were included, similar findings were obtained for the differences in the clinical symptoms between recruits with incidental PEP and those without PEP (data not shown). The severity of symptoms was compared only among confirmed (or plus suspected) cases; we were unable to clarify the effects of PEP on clinical symptoms among milder cases or atypical cases.

To date, it remains unclear whether subjects who have undergone PEP exhibit milder symptoms than those who have not. The results of the present study suggest that PEP does mitigate the severity of measles among young adults (Table 1). Although the effects of PEP were statistically significant, the findings should be confirmed in studies with larger sample sizes, because the present study included only a few cases of measles. Moreover, in the present study, there were 2 suspected cases in recruits with a maximum body temperature of <38.3°C. These recruits had undergone incidental PEP, suggesting that their clinical symptoms were also modified by the vaccination. The mechanism by which PEP modifies the symptoms of measles is still not clear. However, similar effects of PEP have been reported for smallpox, i.e., clinical symptoms are mitigated (4). It is conceivable that the activation of cell-mediated immunity and/or the humoral response by PEP might lead to a shortening of the duration of viremia and to the amelioration of clinical symptoms (5,6).

It should be noted that in the present study, 6 (5 from Camp F and 1 from Camp T) of the 7 recruits without PEP (86%) were the initial to fall ill (i.e., the patients observed in the first wave of the outbreak in the SDF camps), whereas none of the 8 recruits with PEP (0%) were among the first to become sick (Table 1 and Figure 1). Overcrowding, which is defined as the concentration of many susceptible individuals, leads to increased risk of intensive exposure and secondary cases. In this context, it is likely that secondary cases are likely to receive a greater load of measles virus and exhibit more severe clinical symptoms and a higher fatality rate than primary, or index, cases (7). In the present study, recruits who received PEP (all secondary cases) showed milder clinical symptoms than did recruits without PEP (most were initial cases). Thus, the present results may indicate the efficacy of PEP for mitigating the symptoms of measles. Such comparisons should ideally be made among same-generation (or infection-wave) patients; however, we were unable to carry out such comparisons due to the small number of cases in the present study.

Several (8-12) but not all previous studies (13) have suggested that subjects who undergo measles vaccination prior to exposure to the disease exhibit milder clinical symptoms than do those who do not undergo prior vaccination or those in whom the first vaccine has failed. The HI test is not sufficiently sensitive to detect previous immunity. Thus, the apparent attenuation of symptoms by PEP among the recruits observed here might have been due to the effects of prior vaccination or previous unaccounted-for infection or exposure. Although the results of the test for the anti-measles IgM (EIA) antibody were positive in all of the recruits with PEP, the possibility of the presence of measles immunity or secondary vaccine failure (SVF) (wanning immunity after seroconversion) cannot be ruled out, because it has been shown that a positive IgM test does not necessarily indicate the first infection (14).

Measles was prevented in 85% of the recruits (46/54) at Camp F who had undergone incidental PEP. These 54 recruits were residing in a barracks along with the recruits with the initial cases. Most of the HI-negative recruits were immunized, and there were no patients in the third-wave generation at Camp F. Thus, it appears that PEP protected the recruits from subsequent transmission at Camp F. However, the beneficial effects of incidental PEP might be overestimated in this case, because the intensity of exposure might have affected the severity of the measles symptoms (7,8).

As regards non-recruit patients, the symptoms were less severe compared to those of recruits without PEP (Table 1). In addition, the mean age of non-recruit patients was higher than that of recruits. Again, we cannot exclude the possibility that some of these non-recruit patients might have experienced SVF.

In conclusion, young adult measles patients who received incidental PEP exhibited milder clinical symptoms than did young adult patients who had not received PEP.

REFERENCES