

# Very Short Gastroesophageal Acid Reflux during the Upright Position Could Be Associated with Asthma in Children

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## ABSTRACT

**Background:** Gastroesophageal reflux disease (GERD) is diagnosed by the reflux index of 24-hour pH monitoring (pH monitoring). In our previous study, GER episodes during the upright position were more frequent than those during the supine position in asthmatic children. In this study, we investigated the clinical usefulness of the mean hourly number of acid refluxes, designated as the mean number of acid refluxes/hour (h) during the upright position in addition to the pH index for the diagnosis of GERD.

**Methods:** The subjects were 22 preschool asthmatic children. When the reflux index was over 4% or the mean number of acid refluxes/h during the upright position were three times more frequent than those during the supine position even if the reflux index was below 4%, we prescribed famotidine. Children whose asthmatic symptoms improved with famotidine were included in a GERD group. Children who did not meet the criteria by pH monitoring were included in a non-GERD group in asthmatic children.

**Results:** The GERD group was comprised of 9 children. In 2 out of 9 GERD group children, the reflux index was below 4%. The median of the mean number of acid refluxes/h during the upright position was 12.9 in the GERD group, and 3.15 in the non-GERD group. The mean number of acid refluxes/h during the upright position were associated with asthmatic symptoms ( $p < 0.05$ ).

**Conclusions:** Reflux during the upright position was associated with asthmatic symptoms. The mean number of acid refluxes/h during the upright position in addition to the reflux index could be useful in the diagnosis of GERD when associated with asthma.

## KEY WORDS

asthmatic children, gastroesophageal reflux disease, reflux index, spiky reflux, the mean hourly number of acid refluxes during upright position

## INTRODUCTION

The pattern of gastroesophageal acid reflux (acid reflux) episodes depend on body position.<sup>1,2</sup> Generally, it is conceivable that acid reflux episodes tend to increase when a patient is in the supine or prone position (lying-down position). Consequently, in the treatment of gastroesophageal reflux disease (GERD) the upright position is recommended. However, in our

previous study, the frequency of acid reflux during the upright position occurred more often than the frequency during the lying-down position in asthmatic preschool children with GERD. So, we defined parameters of the frequency of acid refluxes as the mean hourly number of acid refluxes (the mean number of acid refluxes/h). The mean number of acid reflux/h during the upright position was 20.0, and that during the lying-down position was 2.62. We showed

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that the pattern of the acid reflux in asthmatic children was different from the pattern which had been recorded as usual. Moreover, in 66.7% of children with GERD, asthmatic symptoms often occurred during the daytime and corresponded with the time when acid reflux could commonly occur.<sup>3</sup> From these results, we speculated that the frequency of acid reflux during the upright position could be related to asthma.

The diagnosis of GERD is based on the reflux index (percentage of total recording time with a pH below 4) during 24-hour pH monitoring (pH monitoring). The baseline of the reflux index is established for diagnosis of GERD. In the present study, we have prescribed antiacid therapy based on this criteria. That is, we prescribed antiacid therapy when the mean number of acid refluxes/h during the upright position was three times more frequent than during the lying-down position even if the criteria of the reflux index was not met. So, we investigated the clinical usefulness of the mean number of acid refluxes/h during the upright position in addition to pH index for diagnosis of GERD in asthmatic children.

## METHODS

We performed pH monitoring between April 2006 and April 2007 in 22 preschool children. All patients had been diagnosed with asthma in our hospital. A diagnosis of asthma was made when patients had more than three episodes of wheezing which were improved by a  $\beta_2$  agonist with or without respiratory infections.<sup>4,5</sup> All participants had no other respiratory disorders, neurological disorders or gastrointestinal symptoms. All had received asthma treatment with the inhaled corticosteroid (ICS) or other treatments. The ICS used was fluticasone or hydrofluoroalkane-beclomethasone dipropionate 200  $\mu$ g bid. The other treatments used were inhaled disodium cromoglicate (DSCG) and/or leukotrien receptor antagonist (LTRA).

The pH monitoring was performed because their asthmatic symptoms could not be controlled by medications. The pH monitoring was performed using a Synectics Digitrapper MKIII (Synectics Medical, Stockholm, Sweden). The probe on the catheter was placed 3–4 cm above the gastroesophageal junction, and its position was confirmed by chest radiography. The asthma medication was continued as usual during pH monitoring.

When the reflux index of pH monitoring was over 4%, we prescribed famotidine (0.5 mg/kg twice daily). And when the mean number of acid refluxes/h during the upright position was three times more frequent than during the lying-down position even if the reflux index was below 4%, we also prescribed famotidine. We defined the parameter of efficacy of famotidine based on whether there was an increasing amount of ICS or also on whether other medication

was prescribed or not. In the case that amount of ICS was not increased and other medication was not prescribed, we defined famotidine as effective.

In the cases that famotidine was effective, we defined the cases with GERD as being associated with asthma clinically. So we divided children into three groups. When asthmatic symptoms were improved by famotidine sufficiently, we defined the cases as the GERD group. When asthmatic symptoms were improved by increasing amounts of ICS or prescribing other medication in addition to famotidine, the extent to which GERD contributed to the asthma symptoms was not known precisely. So, we defined the cases as the not-defined group. On the other hand, when the pH index was below 4% and the mean number of acid refluxes/h during the upright position was not three times more frequent than those during the lying-down position, we defined the cases as those with GERD that was not associated with asthma clinically. These cases were included in the non-GERD group. And, we analyzed the results of pH index and the mean number of acid refluxes/h in the GERD group and the non-GERD group.

In our hospital, asthmatic symptoms are recorded in an asthma diary in order to acquire the precise clinical information. Each doctor wrote recorded in the medical records the time when asthmatic symptoms tended to occur using a diary format. We investigated the medical records which were based on the diary on asthmatic symptoms. And, we divided children into two groups according to asthmatic symptoms. When asthmatic symptoms tended to be worse at night, we defined the cases as the night group. When asthmatic symptoms tended to worse not only at night but also in the daytime, we defined the cases as the day group. And we investigated that the relationship between asthma symptoms and the mean number of acid refluxes/h during the upright position in both groups.

The reason why we used famotidine is that it is the only enteric-coated tablet-type proton pump inhibitors (PPIs) available in Japan. Therefore, PPIs are difficult to use for preschool children, especially those under 5 years of age.

## DATA ANALYSIS

Normal distributed data were presented as mean  $\pm$  SD. Nonparametric data were expressed as median. The differences were assessed by the Mann-Whitney U-test. The percentage between two groups were compared using the Chi-squared test. A *p*-value < 0.05 was considered to be statistically significant for all tests.

## RESULTS

Patient profiles are summarized in Table 1. Famotidine was administered in 14 of 22 children. Among the 14 children, 9 were included in the GERD group.

**Table 1** Patient profiles

|                                       |     |
|---------------------------------------|-----|
| Gender                                |     |
| Male, <i>n</i>                        | 14  |
| Female, <i>n</i>                      | 8   |
| Age, years*                           | 2.0 |
| Medication, <i>n</i>                  |     |
| ICS (200 µg/day)                      | 15  |
| Inhaled DSCG                          | 11  |
| LTRA                                  | 16  |
| Groups by pH monitoring, <i>n</i>     |     |
| GERD                                  | 9   |
| non-GERD                              | 8   |
| not-defined                           | 5   |
| Group by asthmatic symptoms, <i>n</i> |     |
| Night group                           | 12  |
| Day group                             | 10  |

\*Data are presented as median. *n*: number.

ICS, inhaled corticosteroid; DSCG, disodium cromoglicate; LTRA, leukotriene receptor antagonist; GERD, gastroesophageal reflux disease.

**Table 2** Comparison of patient profiles between GERD and non-GERD groups

|                              | GERD group<br><i>n</i> = 9 | non-GERD group<br><i>n</i> = 8 |
|------------------------------|----------------------------|--------------------------------|
| Age, years                   | 1.0*                       | 3.5                            |
| Severity of Asthma, <i>n</i> |                            |                                |
| Severe                       | 6                          | 7                              |
| Moderate                     | 3                          | 1                              |
| Mild                         | 0                          | 0                              |
| Medication, <i>n</i>         |                            |                                |
| ICS (200 µg/day)             | 6                          | 7                              |
| Inhaled DSCG                 | 7                          | 1                              |
| LTRA                         | 7                          | 6                              |

Data are presented as median. \**p* < 0.05, *n*: number.

ICS, inhaled corticosteroid; DSCG, disodium cromoglicate; LTRA, leukotriene receptor antagonist; GERD, gastroesophageal reflux disease.

**Table 3** Comparison of the results of pH monitoring between GERD and non-GERD groups

|   | GERD group<br><i>n</i> = 9 | non-GERD group<br><i>n</i> = 8 |
|---|----------------------------|--------------------------------|
| pH index, %   | 6.80*                      | 1.15                           |
| The mean number of acid refluxes/h during upright position  | 12.9*                      | 3.15                           |
| The mean number of acid refluxes/h during lie-down position | 4.90*                      | 0.60                           |
| Mean duration of one acid reflux, seconds                   | 27.7                       | 21.4                           |

Data are presented as median. \**p* < 0.05

GERD, gastroesophageal reflux disease.

Of the 22 children, 8 were included in the non-GERD group. Of the 22 children who received famotidine, 5 did not demonstrate an improvement in asthmatic symptoms. These patients were included in the not-defined group. A total of 3 children needed ICS on the present medication and 2 children required an increase amount of ICS within less than three months after famotidine was prescribed. In the GERD group, famotidine was prescribed continuously during a median duration of 10 months (data not shown).

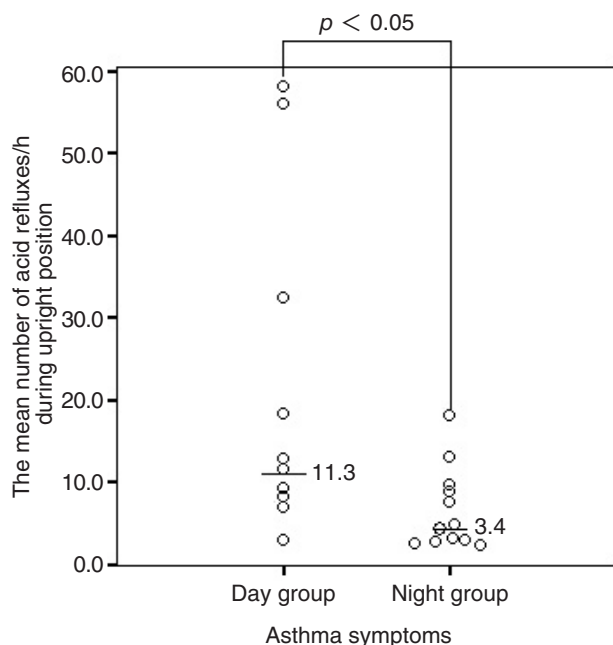
A comparison of patient profiles between the GERD group and the non-GERD group is shown in Table 2. The median age was 1.0 years of age in the GERD group, and 3.5 years of age in the non-GERD group (*p* < 0.05).

A comparison of the results of pH monitoring between the GERD group and the non-GERD group is shown in Table 3. The median of the mean number of acid refluxes/h during the upright position was 12.9 in the GERD group, and 3.15 in the non-GERD group (*p* < 0.05). The median of the mean number of acid refluxes/h during the lying-down position was 4.90 in

the GERD group, and 0.55 in the non-GERD group (*p* < 0.05). There was a significant difference between the median of the mean number of acid refluxes/h during upright and during the lying-down position in the GERD group (data not shown). The median of the mean duration of one acid reflux was 27.7 seconds in the GERD group and 21.4 seconds in the non-GERD group. There was no significant difference between two groups.

The relationship between asthma symptoms and the mean number of acid refluxes/h during the upright position was shown in Figure 1. The median of the mean number of acid refluxes/h during the upright position was 3.40 in the night group, and 11.3 in the day group (*p* < 0.05). Of the 9 GERD group children, 7 were included in the day group. And 7 out of 8 non-GERD group children were included in the night group (data not shown).

The examples of pH monitoring results are shown in Figure 2. The pH monitoring of an asthmatic child with GERD is shown in Figure 2-A. Frequent acid refluxes were recognized. The mean duration of one



**Fig. 1** The relationship between asthma symptoms and the mean number of acid refluxes/h during the upright position.

acid reflux was 22.4 seconds. We defined this very short acid reflux as “Spiky reflux”. The mean number of acid refluxes/h during the upright position was 8.9 and during the lying-down position was 0.8. The pH index was 3.2%. This child had asthmatic symptoms, but had no gastroesophageal symptoms. In contrast, the pH monitoring of a child with GERD who had gastroesophageal symptoms is shown in Figure 2-B. The mean number of acid refluxes/h during the upright position was 15.6 and that during the lying-down position was 24.9. The pH index was 20.7%. The mean number of acid refluxes/h during the upright position was less frequent than during the lying-down position. In particular, there were acid reflux episodes which lasted 5 minutes. We defined this reflux as “Long acid reflux”. The frequency of “Long acid reflux” during the lying-down position was 19. Finally, the pH monitoring of an asthmatic child without GERD was shown in Figure 2-C. Sometime, the Spiky reflux appeared. The median of the mean number of acid refluxes/h during the upright position was 1.8 and during the lying-down position was 0.6. The pH index was 0.3%.

The relationship between the reflux index and the mean number of acid refluxes/h during the upright position in the GERD group and the non-GERD group is shown in Figure 3. In 7 of 9 GERD group children, the reflux index was over 4%. In 2 of 9 GERD group children, the reflux index was below 4%. The mean number of acid refluxes/h during the upright position exceeded 7 in all children of the GERD

group.

## DISCUSSION

The present study was the first to describe the clinical usefulness of the mean number of acid refluxes/h during the upright position in addition to pH index for diagnosis of GERD in asthmatic children. Moreover, this study has shown that the acid reflux pattern could be associated with asthma.

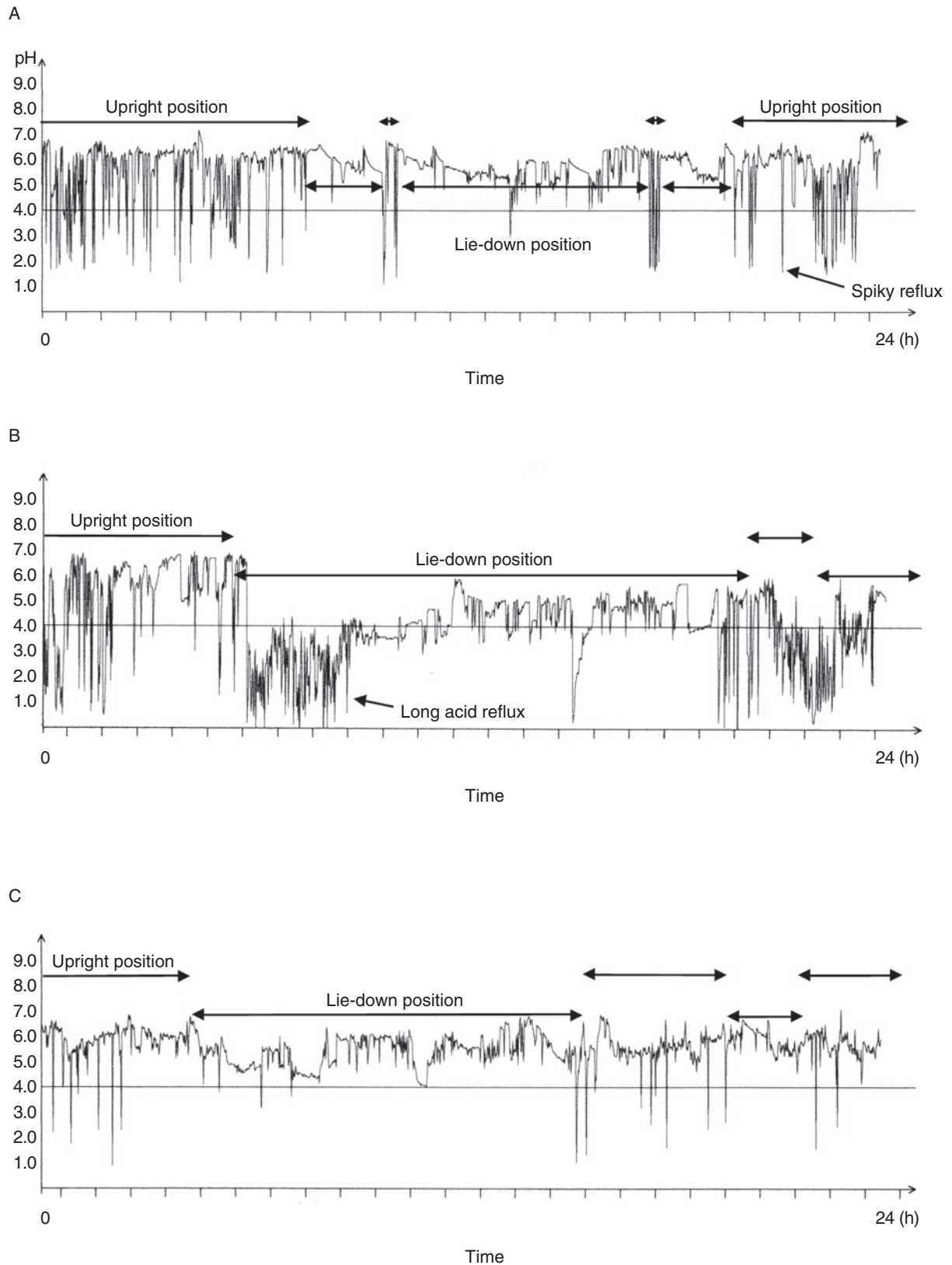
The diagnosis of GERD is based on the reflux index. The cut-off point of the reflux index differed among reports, and ranges from 4% to 6%.<sup>6-9</sup> The 4% cut-off point for the reflux index was recommended by the Japanese guidelines for pH monitoring by the Japanese Society for Pediatric Alimentary Motility. We had performed pH monitoring in preschool children with uncontrolled asthma for the diagnosis of GERD using this criteria. However, on the other hand, the definition of GERD used by gastroenterologists may be very different than that used by allergists who treat asthmatic children.<sup>10</sup> It is possible that the diagnostic criteria of GERD differs between GERD associated with asthma and GERD associated with gastroesophageal symptoms. Therefore, the reflux index may not be useful for the diagnosis of GERD with asthmatic children.

In asthmatic adults, GERD is sometimes diagnosed on the basis of the effectiveness of antacid therapy such as omeprazole before pH monitoring is performed.<sup>11</sup> In the present study, we diagnosed GERD on the basis of the effectiveness of famotidine. As a result, in 2 of the 9 GERD group children, the reflux index was below 4%. This result also suggests that GERD cannot be diagnosed effectively on the basis of the reflux index alone in asthmatic children.

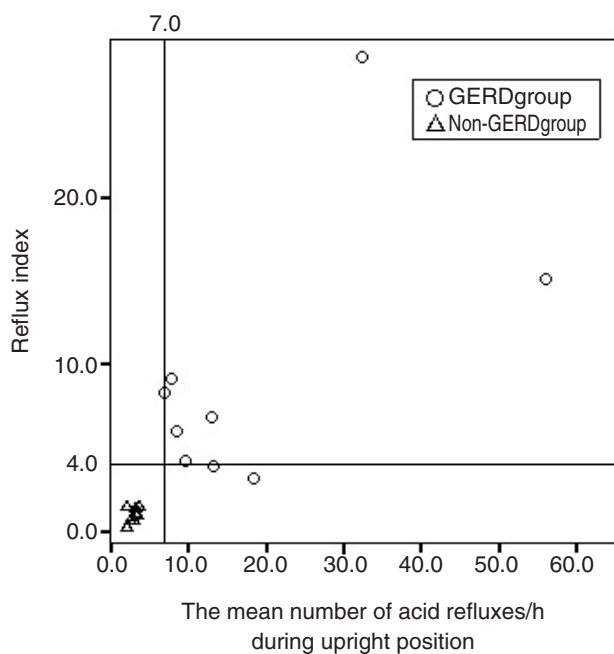
Asthma symptoms are described as ranging from easy to worse during the night (in the lying-down position) according to the Global Initiative for Asthma (GINA) guidelines.<sup>12</sup> However, the number of acid refluxes/h during the upright position were more frequent in the day group than in the night group. In particular, 7 of the 9 GERD group children were included in the day group. In other words, when GERD was associated with asthma, asthmatic symptoms tended to be worse not only at night but also in the daytime. Moreover, there were many acid refluxes during the upright position. The mean number of acid refluxes/h during the upright position was associated with asthmatic symptoms. So, we considered that the index of the mean number of acid refluxes/h during the upright position was important for the diagnosis of GERD when associated with asthma.

In the present study, each acid reflux did not always cause asthmatic symptoms. There are two mechanisms which induce asthma symptoms in children with GERD. One is vagal reflux caused by acid reflux.<sup>13</sup> The other is pulmonary aspiration.<sup>14</sup> Based on the results from the present study showing that

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**Fig. 2** Examples of acid reflux by pH monitoring. **A:** Asthmatic child with GERD, **B:** Child with GERD who had gastrointestinal symptom, **C:** Asthmatic child without GERD.



**Fig. 3** The relationship between the reflux index and the mean number of acid refluxes/h during the upright position of the GERD group and the non-GERD group.

asthmatic symptoms were improved by suppression of acid secretion in the GERD group, we speculated that frequent acid reflux stimulates the esophageal mucosa and supraliminal stimulations of acid reflux caused by vagal nerve reflex. In this manner, the vagal nerve reflex induced asthmatic symptoms. Supraliminal stimulations of acid reflux might be different in every child. However, this remains to be determined.

The esophagitis is one of the most important symptoms of GERD. But, the previous study showed that the presence of esophagitis does not always occur in children with refractory respiratory symptoms and GERD.<sup>13</sup> In an example of a child with gastrointestinal symptom, the “Long acid refluxes” were shown and the acid refluxes during the upright position were less frequent than during the lying-down position by pH monitoring. On the other hand, in an example of an asthmatic child with GERD, “Spiky refluxes” were shown and the acid refluxes during upright position were more frequent than during the lying-down position by pH monitoring. There was an obvious difference in the reflux pattern between an asthmatic child and a child with the gastrointestinal symptoms. We speculated that the difference between the two reflux patterns depended on the presence of esophagitis. But, it has not been clearly elucidated by the present study only.

Respiratory infections can easily exacerbate asthma attacks in young children. Especially, chil-

dren less than 2 years of age are easy to suffer from respiratory infections. The previous report on asthma attack induced by respiratory infections had shown that conventional dose of ICS does not prevent exacerbation of the attack.<sup>15</sup> In the present study, the asthmatic symptoms of the GERD group children whose median age were 1.0 years of age were improved by famotidine. From this result, we speculated that famotidine might be more effective in younger asthmatic children who are easy to suffer from respiratory infections. So, it is important that we diagnose GERD precisely in asthmatic children.

The previous report had shown that the incidence of asthma in children with episodes of recurrent wheezing was 40.4%, and that of GERD was 23.4%. In particular, 57% children with asthma also had GERD.<sup>16</sup> Thus, the incidence of GERD was comparatively high. Therefore, a more sensitive test was needed for the diagnosis of GERD associated with asthma. In the present study, the mean number of acid refluxes/h during the upright position exceeded 7 in all children of the GERD group. There was some possibility that the mean number of acid refluxes/h during the upright position over 7 was the index of diagnosis of GERD associated with asthma. This remains to be determined. Therefore we will investigate whether the mean number of acid refluxes/h during upright position over 7 may be defined as the index of diagnosis of GERD associated with asthma.

We concluded that “Spiky reflux” during the upright position was associated with asthmatic symptoms in children with GERD. And, the mean number of acid refluxes/h during the upright position could be useful in addition to the reflux index for the diagnosis of GERD when associated with asthma.

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