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ARTICLE

Respiratory syncytial virus infection in children with severe motor and intellectual disabilities

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Abstract Children with severe motor intellectual disabilities (SMID) are at high risk of death from acute viral lower respiratory tract infections (LRTI). Although respiratory syncytial virus (RSV) is the most common cause of viral LRTI in children, there have been a few reports on the relationship between SMID and the severity of RSV-LRTI. The aim of the present study is to assess the influence of RSV-LRTI in children with SMID. A case–control study composed of children with SMID (n=18) and previously healthy children (n=43) less than 16 years old hospitalized for RSV-LRTI was performed during five consecutive RSV seasons. The clinical presentation and the laboratory data in the SMID group were compared with those in the non-SMID group. In the bivariate analysis, the median age of the SMID group was higher than that of the non-SMID group (p=0.002). Children with SMID had an increased risk for ventilation support (p=0.057). The count of neutrophils in the SMID group was significantly increased (p=0.012), whereas the proportion of bacterial co-infection was lower than that in the non-SMID group (p=0.005). Multivariate logistic analysis showed that SMID was associated with longer oxygen usage [>7 days: odds ratio (OR) 5.309, p= 0.033]. The present study revealed that children with SMID were prone to developing hypoxia by RSV-LRTI. The strategies for the treatment and prevention of RSV infection need to be improved in SMID children.

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Introduction

Severe motor intellectual disability (SMID) is defined as the combination of severe physical handicap and intellectual disability [1, 2]. Children with SMID generally have obstructive and restrictive respiratory disorders, making it difficult to clear out sputum from the airways, and suffer from multiple-organ disorders, such as muscle weakness, muscle spasticity, seizure, and gastroesophageal reflux, possibly leading to the development of respiratory failure [2, 3]. In addition, the patients are susceptible to recurrent and chronic respiratory infections, which may damage the alveolar tissues. Based on their chronic respiratory condition, these children are susceptible to severe viral lower respiratory tract infection (LRTI) [2].

Respiratory syncytial virus (RSV) is the most common cause of viral LRTI in infants. Almost all children have RSV infection until the age of 2 years, and 2–3 % of them need hospital treatment for RSV-LRTI [4, 5]. It is generally recognized that the morbidity and mortality related to RSV infection is high in premature infants and children with congenital heart disease (CHD) [6, 7]. On the other hand, there are few reports that have analyzed the relationship between children with SMID and RSV infection. The aim of this study is to investigate the severity of RSV-LRTI in children with SMID.

Materials and methods

Study population

Our retrospective case–control study was performed on 61 patients less than 16 years of age who were admitted to the Department of Pediatrics at Kyushu University Hospital during five consecutive seasons from September 1, 2006 to April 30, 2011 for RSV-LRTI. We performed a rapid RSV

antigen detection test for every patient who was suspected to have underlying viral LRTI by physical findings and laboratory data on admission. Eighteen of 61 patients had SMID (SMID group) and the remaining 43 patients did not have any underlying diseases (non-SMID group). SMID was diagnosed according to the classical criteria (Oshima's criteria) [1]. We evaluated the psychomotor development for children under 5 years of age by developmental quotients (DQ) using the Enjoji developmental test, and for those over 5 years of age by intelligence quotients (IQ) using the Wechsler Intelligence Scale for Children. All children with SMID were classified as grade 1 or 2, who were bedridden or able to sit, crawl, or walk with support, and had IQ or DQ lower than 20. The underlying diseases of SMID were as follows: malformation syndrome (n=3), holoprosencephaly (n=2), 21 trisomy (n=2), sequelae of meningitis (n=2), cerebral palsy (n=2), 18 trisomy (n=1), hydrocephalus (n=1), colpocephaly (n=1), lissencephaly (n=1), Aicardi syndrome (n=1), Zellweger syndrome (n=1), and sub-acute sclerosing panencephalitis (n=1). Four of them received tracheostomy and three received home oxygen therapy. Four had congenital heart diseases of non-hemodynamical significance. In none of the enrolled patients was any primary or secondary immunodeficiency identified. Clinical information on each patient was collected using a standardized case report form. Many of the enrolled patients had histories of aspiration pneumonia complicated by gastroesophageal reflux disease (GERD), but none of them had apparent episodes of aspiration by GERD at the onset of RSV-LRTI. All patients had regular dental examinations, and none of them were under dental treatment at the onset of RSV-LRTI. From the laboratory data on admission were examined peripheral white blood cell (WBC) counts and neutrophil counts, serum C-reactive protein (CRP) levels, the findings of chest X-ray, and the bacteriology results of sputum samples. We diagnosed the patients as having LRTI when they had cough and sputum production as clinical symptoms with auscultatory findings of abnormal breath sounds, wheezes, or crackles [8]. None of the patients had typical symptoms of chronic sinusitis, such as yellow or greenish discharge from their noses.

Confirmation of RSV infection

All the patients were diagnosed as having RSV infection by a rapid antigen detection test (SA Scientific, San Antonio, SA, USA) using a nasopharyngeal aspirate or secretion suctioned through the tracheostomy orifice. It has been reported that specimens obtained by endotracheal tube aspiration had a higher sensitivity for the RSV antigen detection than by nasopharyngeal aspirate specimens in adult patients [9]. To the best of our knowledge, there have been no similar studies in child patients. Nevertheless, it would be rational to speculate that there was little practical difference in the sensitivity of antigen detection by specimens from nasopharyngeal aspiration and from endotracheal tube aspiration, because the RSV viral load in the nasopharyngeal lesions was significantly greater in child patients than that in adults. A previous report demonstrated that the specificity of the test was equally high by specimens from nasopharyngeal or endotracheal tube aspiration [9]. It had also been reported that the rapid RSV antigen detection test had a lower sensitivity than viral culture or reverse transcriptase polymerase chain reaction (RT-PCR) [10, 11]. To confirm the sensitivity of the rapid antigen RSV detection test, we also performed multiplex RT-PCR assay by using samples from eight patients. The viral RNA was extracted using a Ribospin vRD kit (GeneAll, Seoul, Korea), in accordance with the manufacturer's instructions. Multiplex RT-PCR was conducted using the Seeplex® RV15 OneStep ACE Detection kit (Seegene Inc., Seoul, Korea). Reverse transcription and PCR amplification were performed on the GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA, USA). Amplicons were separated and detected by the automated microchip electrophoresis system MultiNA (Shimadzu, Kyoto, Japan). RSV A or B were detected with all samples, while eight samples with negative results were detected by the rapid RSV antigen test, analyzed by RT-PCR, and it was found that all of them were negative. Based on this result, the sensitivity of the rapid RSV antigen test corresponded with that of the RT-PCR assay, indicating that the rapid antigen test would be a reliable diagnosis method.

Sputum collection, bacteriological examination, and its evaluation

Sputum samples were obtained for the confirmation of bacterial infection. The sputum collection and the judgment of their qualities using Geckler's classification were performed as previously described [12]. Smears, classified as Geckler's group 4 or 5, were judged to be suitable for bacterial examination. Only sputum samples suctioned through the tracheostomy orifice were judged to be suitable, even when they were classified as Geckler's group 6. When phagocytized bacterial cells were seen on the Gram stain smear of the sputum sample and corresponding bacterium was isolated later, it was identified as a complication of bacterial infection.

Statistical analysis

The two-sample t-test with unequal variants was used to calculate the difference in WBC and neutrophils counts. Because WBC and neutrophils counts were distributed with right-skewness, log-transformed values were used in the statistical analysis. The Wilcoxon Mann–Whitney method

was used to compare other continuous variables. Fisher's exact test was applied for the qualitative analysis. The multivariate logistic regression analysis was performed to estimate odds ratios (ORs) for the association between the independent variables and outcomes. *p*-values less than 0.05 were considered to be statistically significant.

STATA (version 11.1; StataCorp, College Station, TX, USA) was used for the multivariate logistic regression analysis and JMP (version 9.0; SAS Institute Inc., Cary, NC, USA) was used for the remaining analyses.

Results

The patients' clinical characteristics and laboratory data are shown in Table 1. Wheezes were detected by chest auscultation in all of the enrolled patients. None of these patients died in the present study. In the bivariable analysis, the median age of the SMID group was higher than that of the non-SMID group (p=0.002). The count of neutrophils was significantly increased in the children with SMID (p=0.012). In 29 (55.8 %) of 52 patients from whom sputum samples could be obtained, the sputum samples were enough to be evaluated by bacterial examination. In 15 (51.7 %) of the 29 sputum samples, one or more bacterial pathogens were identified. One patient (11.1 %) in the SMID group and 14 patients (70 %) in the non-SMID group were diagnosed as having bacterial co-infection, respectively. Samples from nasopharyngeal aspirate were obtained from six of nine SMID patients for bacterial study, and we found that only one patient was diagnosed as having bacterial co-infection (16.7 %). Compared with the non-SMID group, the ratio of bacterial co-infection was lower in the SMID group (p=0.005). First, an oxygen administration was performed for all of the patients with hypoxic state. A respirator support was introduced next for the patients who continued to be in hypoxic and hypercapnic state, even with the oxygen therapy. The number of children who required mechanical ventilation was 4 (22 %) in the SMID group and 2 (5 %) in the non-SMID group, respectively. The causes of requiring ventilation were acute respiratory failure (n=5) and frequent apnea (n=1, non-SMID group). More children with SMID required mechanical ventilation for respiratory support due to RSV-LRTI (p=0.057).

Multivariate logistic regression analysis was performed to exclude the bias due to the differences in clinical characteristics. The severity of RSV-LRTI in the patients with SMID was estimated by longer supplemental oxygen (over 7 days), longer hospitalization (over 9 days), and requirement of mechanical ventilation (Table 2). The patients with SMID were significantly associated with longer supplemental oxygen (OR 5.309, p=0.033). The risks of longer hospitalization and requiring mechanical ventilation also became higher, but they did not reach statistical significance (Table 2).

Supplemental oxygen therapy exceeded 7 days in eight patients with SMID. The underlying diseases of the patients were malformation syndrome (n=2), sequelae of meningitis (n=1), cerebral palsy (n=1), 18 trisomy (n=1), hydrocephalus (n=1), colpocephaly (n=1), and sub-acute sclerosing panencephalitis (n=1). There were no significant differences in the proportions of patients who received tracheostomy and home oxygen therapy and having congenital heart diseases of non-hemodynamical significance between the patients who received supplemental oxygen for more or less than 7 days. The proportion of patients diagnosed as having pneumonia was higher in SMID patients who received supplemental oxygen for over 7 days (62.5 %), while this proportion was also higher in the patients without underlying disease (54.5 %).

Discussion

Children with SMID, which is not a worldwide recognized population, are similar to children with neuromuscular impairment (NMI) in having difficulty to cough up sputum. SMID is defined by the presence of severe "neuromuscular impairment" and intellective disability. NMI was an independent risk factor with increased risks for pediatric intensive care unit (PICU) admission and respiratory failure due to RSV-LRTI [3]. Keren et al. also showed that neurological and neuromuscular disease was a risk factor of respiratory failure in children with influenza [13]. In the present study, we investigated whether children with SMID were prone to developing severe LRTI in the patients with RSV infection, the most common cause of viral LRTI in childhood. The duration of supplemental oxygen was longer by RSV-LRTI in children with SMID compared with patients without underlying diseases. In SMID patients, hypoxemia can easily occur by increased sputum production on acute viral respiratory infection because of their inadequate coughing to expectorate sputum.

Bacterial co-infection had been a risk factor for severe RSV-LRTI among previously healthy children [14]. Up to 40 % of the patients with RSV bronchiolitis, who required PICU admission and mechanical ventilation, had bacterial co-infection [14]. In the present study, only 11 % of SMID patients hospitalized for RSV-LRTI had bacterial co-infection, while 70 % of the patients without underlying diseases had co-infection. To our best knowledge, there has been no report in the literature that has examined the relationship between bacterial co-infection and the severity of RSV-LRTI in patients with SMID or NMI. There is a limitation to the utility of sputum sample because of the difficulty to expectorate adequate sputum in pediatric

Table 1 Comparison of demographic, clinical, and laboratory variables in relation to respiratory syncytial virus (RSV) infection between patients with and without severe motor intellectual disabilities (SMID)

	Patients with SMID (n=18)	Patients without SMID (n=43)	p-Value
Age, months (range)[a]	21 (2–33)	8 (0–31)	*0.002*
Gender, % male[a]	50	53	0.804
Duration of supplemental oxygen, days (range)[a,b]	10 (5–37)	8 (1–15)	0.15
WBC counts, /μl (range)[a]	11,603 (8,838–15,233)	9,636 (8,314–11,168)	0.221
Neutrophil counts, μl (range)[a]	6,415 (4,246–9,694)	3,472 (2,722–4,428)	*0.012*
Serum CRP levels, mg/dL (range)[a]	2.93 (0.11–11.18)	2.24 (0.02–12.78)	0.169
Use of antimicrobial agents, %	78	51	0.054
Bacterial co-infection, %	11 (n=9)	70 (n=20)	*0.005*
Pneumonia, %	44	44	0.602
Duration of supplemental oxygen>7 days, %[b]	44	21	0.602
Duration of hospitalization>9 days, %[b]	56	35	0.113
Mechanical ventilation, %	22	5	*0.057*

[a] The median value was used

[b] For the patients receiving home oxygen therapy, the duration of supplemental oxygen was defined as when the dose of oxygen returned to the original amount

patients. However, some reports showed the usefulness of the identification of the causative pathogen using sputum samples taken using special procedures [11, 15]. In our previous study, many samples suctioned from the hypopharynx through the nose were also classified as being suitable for bacterial examination without being washed [12]. It is possible that even RSV infection without bacterial co-infection will easily cause severe LRTI in children with SMID.

A multicenter randomized double-blind placebo-controlled trial showed the efficacy of the humanized monoclonal antibody palivizumab to prevent severe RSV infection in infants born before 35 weeks of gestation and children with hemodynamically significant congenital heart disease [6, 7]. Palivizumab prophylaxis is also recommended for children with NMI [3]. However, the usage of palivizumab for that population is still off-label in most countries. Even beyond infancy, SMID patients are prone to developing severe LRTI. It is difficult to determine until what age palivizumab prophylaxis should continue. Many researchers have tried to develop a vaccine against RSV but none have been successful to date [16]. It is expected that a safe and effective vaccine can be developed to prevent severe RSV infection.

The neutrophil count was significantly increased in children with SMID, in spite of the low bacterial co-infection rate. According to the clinical records for the SMID and non-SMID patients, the neutrophil counts in the steady state were not increased in both groups. Although the exact reason for neutrophilia in SMID remains unknown, it might be possible that an acute stress by RSV infection induced the transient increase of neutrophils in peripheral blood for the SMID patients, who are considerably sensitive to acute stress by viral infection or respiratory failure.

This retrospective study has some limitations. First, we did not perform other virological tests in order to detect other respiratory viruses except RSV. In infants with RSV bronchiolitis, some reports showed similar clinical progression for co-infections and single infection, whereas others suggested that co-infection might increase the severity of the disease [17, 18]. Further investigations are warranted in order to evaluate the severity of RSV-LRTI with viral co-infection in SMID children. Second, only the inpatients with RSV infection were included in this study. We could not

Table 2 Multivariate analysis of the relationship between the severity of respiratory syncytial virus lower respiratory tract infections (RSV-LRTI) and severe motor intellectual disabilities (SMID)

Indicator of severe infection	Odds ratio	95 % confidence interval	p-Value
Duration of supplemental oxygen>7 days[a]	5.309	1.195–27.225	*0.033*
Duration of hospitalization>9 days	2.544	0.677–10.294	0.172
Mechanical ventilation	5.100	0.769–46.473	0.104

[a] For the patients receiving home oxygen therapy, the duration of supplemental oxygen was defined as when the dose of oxygen returned to the original amount

perform a population-based study and compare the overall clinical manifestation between these groups. Third, the study in our hospital alone may bias the patient population because Kyushu University hospital is a tertiary referral hospital in the Fukuoka area. Finally, the present study was performed in a single medical center, and the total number of patients in the study population was small. The small number of children in each group may lead to inaccuracy of the statistic analysis to detect differences between the groups.

In conclusion, children with SMID were at high risk of developing hypoxia by RSV-LRTI. We should treat these children based on the recognition that they are prone to developing hypoxia by viral infections because of their chronic respiratory failure. A large-scale prospective study is warranted to validate the severity of single RSV infection in children with SMID.

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Conflict of interest The authors declare that they have no conflict of interest.

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