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Significance of 25-hydroxy vitamin D in early infants infected with respiratory syncytial virus

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Abstract

Background

25-Hydroxy Vitamin D deficiency at birth has been reported as a risk factor for respiratory syncytial virus (RSV) infection in children. Alternatively, the association between 25-Hydroxy Vitamin D deficiency and disease severity remains unclear. We hence analyzed the clinical features of patients with 25-Hydroxy Vitamin D and RSV infection in Tokyo, Japan.

Methods

The subjects were 15 infants of less than 3-months old, who had RSV infection and were admitted to Tokyo Medical University Hospital between November 2012 and July 2021. As controls, 8 infants of less than 3-months old, who were admitted to the hospital during the same period for viral infections other than RSV or fever after vaccination were included in the study. Serum 25-Hydroxy Vitamin D levels were measured at the time of admission, and clinical features were retrospectively reviewed from medical records. We also analyzed the correlation between the level of production of cytokines and chemokines, which influence the possible severity of RSV infection, and the concentration of active vitamin D in peripheral whole blood stimulated with RSV antigen.

Results

No association was observed between serum 25-Hydroxy Vitamin D level on admission and clinical picture of RSV infection. Patients hospitalized for RSV infection had lower serum 25-Hydroxy Vitamin D levels than the controls, although the difference was not statistically significant ($p = 0.293$). In addition, this study design did not clarify whether 25-Hydroxy Vitamin D changes the production of cytokines and chemokines.

Conclusion

In infant patients in Japan, 25-Hydroxy Vitamin D deficiency was not associated with the severity of RSV infection. Further clinical evaluation and immunological investigation of the changes induced by 25-Hydroxy Vitamin D are required.

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Introduction

RSV is a major cause of bronchitis in children under 1 year of age. Almost all children are affected at least once by the age of 2 to 3 years, and repeated infections are common[1-3]. Most affected infants spontaneously recover with only common cold symptoms that do not require hospitalization. On the other hand, Mazur et al. reported that 33 million children under the age of 5 years were estimated to have lower respiratory tract RSV infections worldwide in 2005, of which 3 million were hospitalized and 66,000 to 199,000 died[4].

The treatment of RSV infection is mainly symptomatic, and effective therapeutic agents and vaccines for its prevention are still under development. Risk factors of severe RSV infection have been reported to be low birth weight, preterm birth, male infant, maternal smoking, presence of compatriots, allergic predisposition, and not being breast-fed[5]. However, in clinical practice, we experience many exceptions. Therefore, clarification of the risks of morbidity and severity of RSV infection and the development of appropriate preventive and therapeutic interventions are crucial.

25-Hydroxy Vitamin D, when taken up intracellularly via the 25-Hydroxy Vitamin D receptor, has nongenomic effects on the immune system[6]. Recently, 25-Hydroxy Vitamin D deficiency at birth, defined as an umbilical cord blood 25-Hydroxy Vitamin D level of less than 20 ng/ml, was reported to be a risk factor for the susceptibility to lower respiratory tract RSV infection in the first year of life[7]. Some reports showed an association between 25-Hydroxy Vitamin D deficiency at the time of RSV infection and the severity of illness from RSV infection[8], whereas other studies did not[9], suggesting that there is still no definitive consensus on this issue. We also previously measured serum 25-Hydroxy Vitamin D levels at the time of admission, and assessed the severity of RSV infection in children younger than 3 months of age who were hospitalized with RSV infection in Tokyo, Japan[10]. We found that 25-Hydroxy Vitamin D levels had no effect on the severity of RSV infection.

It has also been reported that the production of cytokines and chemokines is associated with the severity of RSV infection. RSV infection of the tracheal epithelium results in the secretion of chemokines, such as Regulated on Activation Normal T Cell Expressed and Secreted (RANTES), Interleukin-8 (IL-8), and Macrophage Inflammatory Protein-1α (MIP-1α), which in turn induce chemotaxis by neutrophils and eosinophils. This leads to severe inflammation, edema, and narrowing of the lower airways, causing wheezing and bronchitis[11-13].

We previously reported that the cytokine profiles of nasal secretions from RSV-infected patients showed significantly higher levels of IL-8 in the severe disease group than in the less severe disease group. In a comparison of the severity of IL-8-251T/A Single Nucleotide Polymorphisms (SNPs), the frequency of the A allele was significantly different in the RSV infection group compared with controls[14]. There is a systematic review evaluating the response to the addition of 25-Hydroxy Vitamin D in both human cell lines and Peripheral Blood Mononuclear Cells (PBMCs), which reported an inhibition of the production of IL-8, IL-6 and Monocyte Chemoattractant Protein-1 (MCP-1)[15]. On the other hand, there have been no reports showing how active 25-Hydroxy Vitamin D is involved in the production and inhibition of cytokines and chemokines in patients with RSV infection.

In the present study, firstly, as a clinical study, the previously performed association between 25-Hydroxy Vitamin D deficiency and the severity of RSV infection was re-evaluated in additional cases. Then, as an immunological evaluation, RSV antigen was added to peripheral whole blood of adults, RSV repeat infections, severe RSV infections, and non-RSV infected cases who had specimens available and agreed to the study, and the cytokines and chemokines produced were measured, and the changes occurring after the addition of active 25-Hydroxy Vitamin D were observed. We then investigated the TA 251 SNPs, which has been reported to be involved in the secretion of IL-8[16-18].

Materials and Methods

25-Hydroxy Vitamin D levels and severity of RSV

The subjects were 15 Japanese infants less than 3 months of age with RSV infection, who were admitted to Tokyo Medical University Hospital between November 2012 and July 2021. Exclusion criteria were preterm infants, low birthweight infants, and infants with congenital diseases (congenital heart disease, chromosomal abnormalities, etc.). All decisions regarding treatment during hospitalization were made by the attending physician, and were unassociated with this study.

As controls, 8 infants between day 14 and 3 months of age who were admitted to the hospital during the same period for viral infections other than RSV or fever after vaccination were included in the study.

Serum 25-Hydroxy Vitamin D levels were measured by the chemiluminescent enzyme immunoassay method at the time of admission, and serum 25-Hydroxy Vitamin D deficiency was defined as a level less than 20 ng/ml. Clinical profile (hospital stay, respiratory management, clinical score, white blood cell count, blood gases, and N-terminal pro-natriuretic peptide (NT-proBNP)) were reviewed retrospectively from the medical records.

The severity of the RSV infection was determined using the clinical score, which is the sum of the respiratory disorder score and disorder of daily living score,

which is routinely used in Japan[19].

The respiratory disorder score includes SpO_2, respiratory rate, expiratory wheezing, and sink breathing. Each was rated on a scale of 0 to 2, resulting in a total score of 0 to 8 (mild, moderate, and severe). The disorder of daily living score includes oral intake and sleep. Each is rated on a scale of 0 to 2, resulting in a total score of 0 to 4 (mild, moderate, and severe). The total clinical score was from 0 to 12, with 0 to 6 defined as mild, 7 to 10 as moderate, and 11 to 12 as severe. Peripheral blood or nasal fluid of the subjects was also collected to isolate genomic Deoxyribonucleic Acid (DNA) to determine the IL-8-251A/T polymorphism. The IL-8-251A/T polymorphism was analyzed by restriction fragment length polymorphism (RFLP) followed by polymerase chain reaction (PCR).

Analysis of cytokine and chemokine levels

The RSV antigen was added to 5 samples of peripheral whole blood (200 μL ; different from the samples in the clinical analysis above), cultured for 0, 24, and 48 hours, and the cytokines and chemokines produced were measured. As the RSV antigen, a split antigen made by infecting Vero cells with a strain of subgroup A isolated in 2004 was used. In addition, we cultured cells with RS antigen under medium with active 25-Hydroxy Vitamin D at the same time, at concentrations of 100 μg/ml and 10,000 μg/ml, and the changes were observed in the culture medium for 0, 24, and 48 hours. The cytokines and chemokines produced were assayed for 27 items using the Bio-Plex Multiplex Cytokine Assay. Items are IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Interferon-γ (IFN-γ), Tumor Necrosis Factor-α (TNF-α), Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF), MCP-1, Macrophage Inflammatory Protein-1β (MIP-1β), Granulocyte Colony Stimulating Factor (G-CSF), Vascular Endothelial Growth Factor (VGEF), Platelet-Derived Growth Factor (PDGF), Eotaxin, Fibroblast Growth Factor (FGF), Interferon gamma-induced protein-10 (IP-10), Macrophage Inflammatory Protein-1α (MIP-1α), RANTES. Peripheral blood or nasal fluid was collected from 5 patients, and DNA was isolated. The IL-8-251A/T polymorphism was analyzed by PCR followed by restriction RFLP[16].

Statistical analysis

All statistical analyses were performed using IBM® SPSS® statistics version 27, and a *p*-value of less than 0.05 was considered to indicate a statistically significant difference between groups. A Pearson's correlation coefficient and Spearman's rank correlation coefficient of more than 0.8 was considered to indicate a statistically significant correlation (*p*-value < 0.05).

Ethics

This study was approved by the Medical Ethics Review Committee of Tokyo Medical University (study approval no. : SH3841). Informed consent for participation in the above clinical and laboratory studies was obtained from the parents or the individual.

Results

25-Hydroxy Vitamin D levels and severity of RSV

Table 1 shows the characteristics of the 15 patients. The patients were 10 boys and 5 girls ; 4 infants (cases 2, 7, 9, and 12) were born in August, 3 infants (cases 5, 11, and 13) were born in May, 3 infants (case 3, 6, and 15) were born in June, 2 infants (cases 4 and 10) were born in July, and 1 patient each was born in April, November, and December. All patients were born between 37 to 40 weeks, and their birth weights were 2,592 to 3,270 g. Table 2 shows the patients' diagnoses (pneumonia or bronchitis), serum 25-Hydroxy Vitamin D levels, and clinical features. Four patients (cases 4, 5, 11, and 12) had pneumonia and 11 had bronchitis ; 10 patients (cases 1 to 10) had 25-Hydroxy Vitamin D deficiency with serum levels of less than 20 ng/ml. Case 9 was intubated and managed using a ventilator, patient 2 was managed with noninvasive positive pressure ventilation, patients 3 and 5 were managed with high-flow nasal cannula oxygen, and the other 8 patients did not require respiratory management. The association between the serum 25-Hydroxy Vitamin D level measured at the time of admission and each of the items was analyzed, but no correlation was found using Pearson's correlation coefficient or Spearman's rank correlation coefficient (Table 3).

A comparison of serum 25-Hydroxy Vitamin D levels

Table 1. Patient characteristics

Case	Sex	Month of birth	Weeks of gestation	Birth weight (g)	Age on admission (months)
1	M	November	40	3,028	1
2	F	August	40	2,970	I
3	F	June	38	3,160	Day 18
4	M	July	38	3,184	2
5	M	May	38	2,680	1
6	M	June	38	2,978	2
7	F	August	37	2,682	1
8	M	December	39	2,850	3
9	M	August	38	2,750	Day 29
10	M	July	38	3,246	Day 16
11	F	May	38	3,530	1
12	F	August	37	3.050	2
13	M	May	37	2,592	2
14	M	April	40	3,032	2
15	M	June	39	3,270	3

Table 2. Serum vitamin D levels and clinical characteristics of the patients

No.	Semm vitaminD (ng/mL)	Clinical score	Diagnosis	Respiratory management	Days in hospital	WBC (/μL)	Hb (g/dL)	CRP (mg/dL)	RR (/min)	SpO_2 (%)	PCO_2 (mmoL/L)	HCO_3^- (mmoL/L)	NT-proBNP (pg/dL)	IL-8-251A> T
1	<4	4	Bronchitis	None	5	6.000	10.9	<0.3	60	96	45.5	25.1	325	ND
2	<4	7	Brnnchitis	NPPV	7	7,200	11.9	<0.3	48	100	49.1	27.8	562	ND
3	<4	4	Bronchitis	HFNC	10	9,500	12.3	0.3	48	96	40.9	23.7	ND	AT
4	7.2	3	Pneumonia	None	7	13,400	11	<0.3	42	98	43.2	22.4	2,030	ND
5	10.4	4	Pneumonia	HFNC	9	9,300	10.1	0.3	40	96	57.4	24.6	ND	TI
6	11.5	1	Bronchitis	None	3	5,200	9.2	<0.3	36	100	42.7	23.3	741	ND
7	13	5	Bronchitis	None	6	8,100	12.3	<0.3	36	100	42.1	21.4	153	ND
8	16.5	6	Bronchitis	None	5	16,600	11.5	4.3	32	87	43.1	24.8	84	ND
9	17.8	11	Bronchitis	Mechanical ventilation	12	10,100	11.2	1.1	68	84	60.7	29.1	4,090	ND
10	18	1	Bronchitis	None	8	8,900	11.9	0.3	36	98	36.9	22.5	ND	ND
11	24.2	2	Pneumonia	Venturi mask	7	7,300	12	0.3	48	96	49.2	25.5	ND	TI
12	25.5	3	Pneumonia	Venturi mask	7	13,200	10.3	2.2	48	99	40.6	25.1	272	ND
13	25.5	2	Bronchitis	None	5	7,400	10.5	0.3	38	100	43.7	24.2	ND	ND
14	26.6	2	Bronchitis	None	4	14,000	11	1.1	42	97	37.3	23.7	ND	TI
15	29.8	6	Bronchitis	Venturi mask	8	13,200	9.6	3.6	52	94	50.2	26.5	137	ND

NPPV, noninvasive positive pressure ventilation ; HFNC, high-flow nasal cannula oxygen

between patients and controls demonstrated that RSV-infected children tended to have lower 25-Hydroxy Vitamin D levels, although there was no statistically significant difference (Fig. 1).

Analysis of cytokine and chemokine levels

The background characteristics and IL-8-251A/T polymorphisms of the 5 patients are shown in Table 4. Four of the 5 patients had the AT allele which has been reported to correlate with high protein expression and a high neutrophil chemotaxis index.

Table 3. Serum vitamin D levels and clinical characteristics analyzed by Pearson's correlation coefficient or Spearman's rank correlation coefficient

		age	Month of birth	Birth weight (g)	Days in hospital	WBC (/μL)	Hb (g/dL)	RR (/min)	PCO_2 (mmoL/L)	HCO_3^- (mmoL/L)	Clinical score
Serum vitamin D (ng/mL)	Pearson's correlation coefficient	0.435	-0.367	0.133	-0.1	0.379	-0.297	-0.5	0.068	0.118	−0.142
	Significance probability (two-sided)	0.105	0.178	0.637	0.724	0.163	0.283	0.859	0.809	0.118	0.613

		Bronchitis v.s. Pneumonia	Respiratory management	CRP (mg/dL)	SpO_2 (%)	NT-proBNP (pg/dL)
Serum vitamin D (ng/mL)	Spearnan's rank correlation coefficient	0.018	-0.152	0.686	-0.096	-0.377
	Significance probability (two-sided)	0.951	0.59	0.005	0.734	0.318

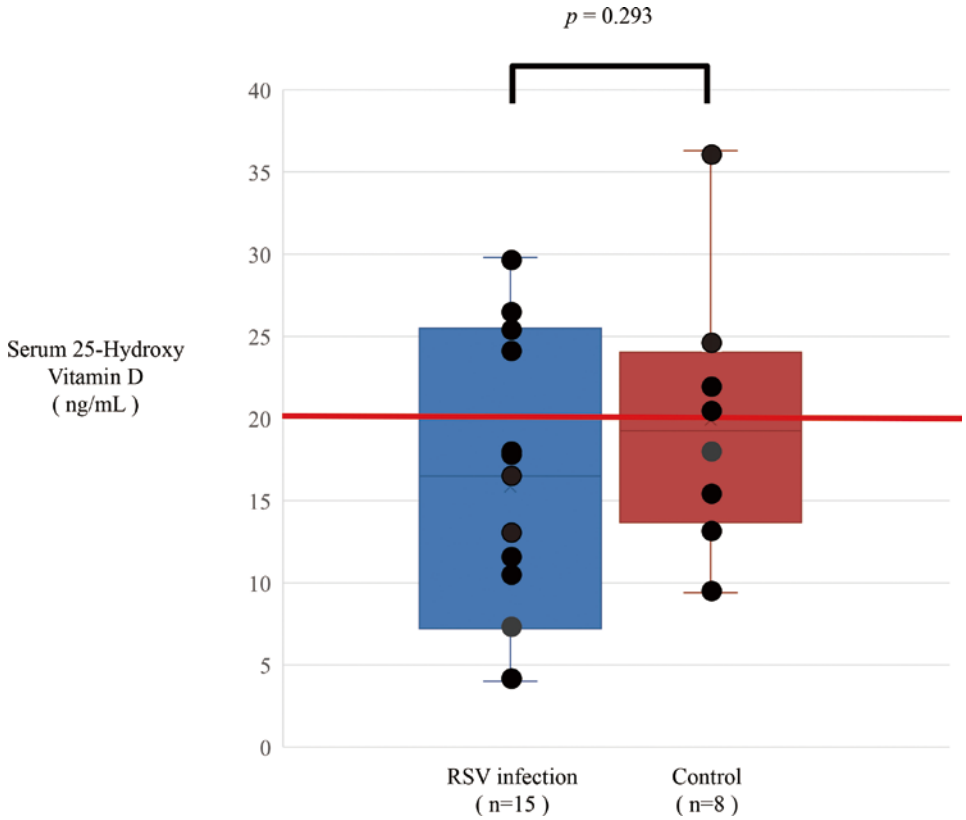


Fig. 1. Comparison of serum 25-Hydroxy Vitamin D levels between hospitalized RSV-infected patients and controls
Controls comprised hospitalized patients of less than 2 months of age, who were not infected with RSV. Serum 25-Hydroxy Vitamin D levels were low in both RSV-infected patients and controls. There was no significant difference in serum 25-Hydroxy Vitamin D levels between hospitalized RSV-infected patients and controls. The boxes in the graph indicate the first quartile and third quartile, and the bars indicate maximum, the second quartile, and minimum values. Statistical analysis was performed using the unpaired t-test. There was no statistically significant difference between the 2 groups.

Table 4. Characteristics and the IL-8-251A/T polymorphism of 5 patients

Case	Age (years)	Characteristic	Analysis sample	IL-8-251A>T
A	4	History of severe RSV infection	Lymphocyte	AT
B	11	Tabes dorsalis without immunodeficiency	Lymphocyte	AT
C	2	History of severe RSV infection	Nasal discharge	TT
D	4	History of recurrent RSV infection	Lymphocyte	AT
E	Adult	Control	Lymphocyte	AT

Changes in cytokines and chemokines produced by the addition of the RSV antigen and 25-Hydroxy Vitamin D to peripheral whole blood are shown in Fig. 2. In patients A and B the production of IL-8 tended to be suppressed in a 25-Hydroxy Vitamin D concentration-dependent manner. However, the same tendency was not observed for other cytokines and chemokines, and no consistent tendency was observed upon analysis of the overall results, including other patients. Therefore, the production of these cytokines did not clearly correlate with the IL-8-251A/T polymorphism.

Discussion

In this study, we found no significant association between serum 25-Hydroxy Vitamin D level and clinical features of the patients hospitalized for RSV infection in the Tokyo area. Although there was no significant difference, patients hospitalized for RSV infection tended to have lower serum 25-Hydroxy Vitamin D levels than control subjects. We suspect that 25-Hydroxy Vitamin D deficiency may be a risk factor for RSV infection, but does not affect the severity of the disease.

25-Hydroxy Vitamin D deficiency has been reported in many countries and regions, and is a worldwide problem[20-21]. It has also been reported to be a risk factor for preterm birth, rickets, type 1 diabetes, schizophrenia, sleep disorders, bronchial asthma, autism spectrum disorders, some malignant neoplasms, and respiratory infections, and is hence a disease that needs to be addressed[22-28].

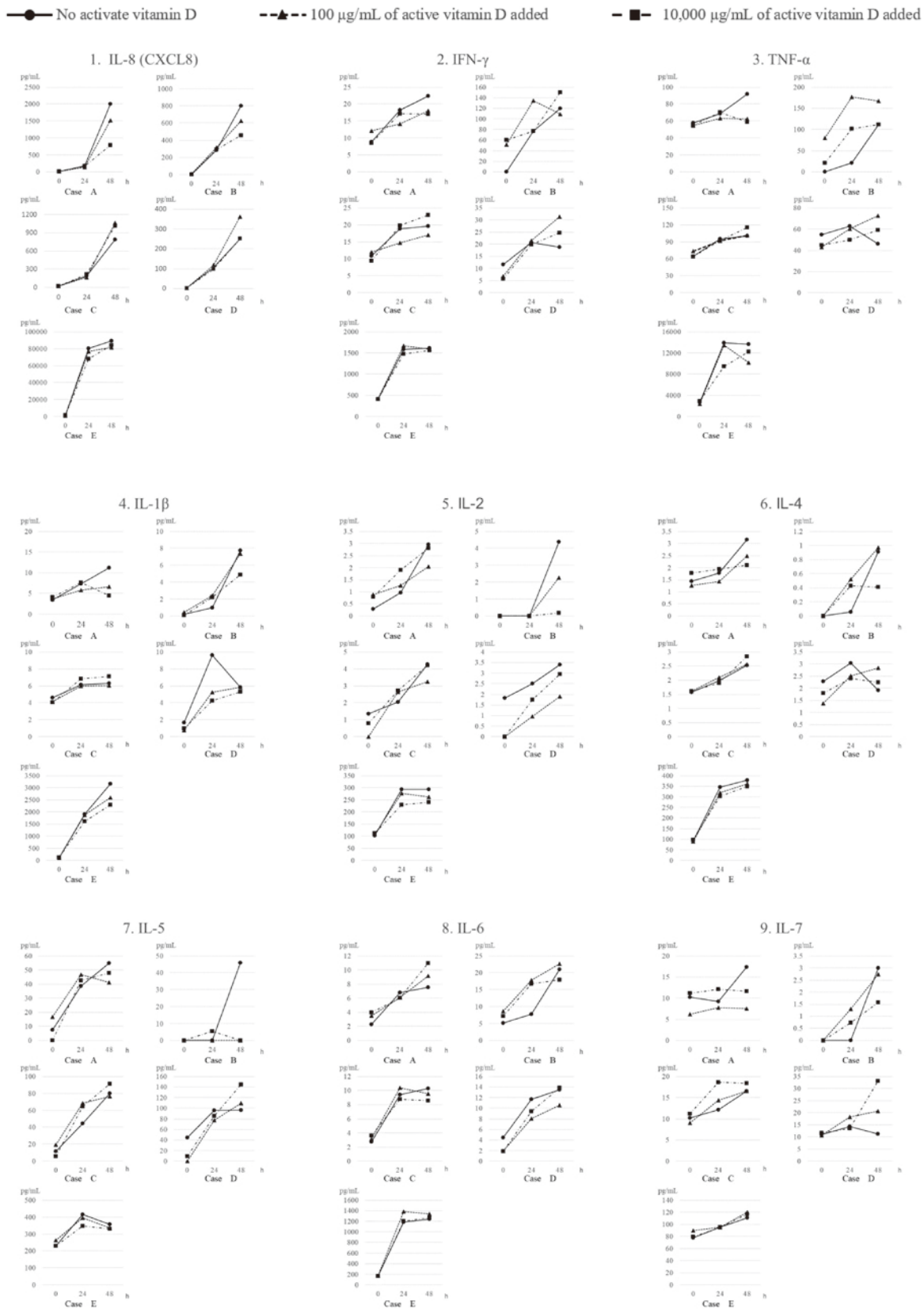
As 25-Hydroxy Vitamin D deficiency is thought to be primarily a result of diet (including breast milk/artificial milk and supplements), ultraviolet exposure, and genetic predisposition, it may be strongly affected by culture, region, and race, and therefore, the results of various studies should be interpreted with caution.

Beigelman et al. reported that there was no association between serum 25-Hydroxy Vitamin D levels on admission and severity of illness in children under 1 year of age hospitalized for RSV bronchitis[9]. This study included 46% Caucasians and 42% African-Americans in the United States, and reported that 25-Hydroxy Vitamin D deficiency was observed in early infants and breastfed infants, but was not more common than in the general infant population. Although the point of interest is somewhat different from that of our study, which included only infants in the early postnatal period, the results of this previous study indicate that there is no association between 25-Hydroxy Vitamin D deficiency and the severity of RSV infection.

On the other hand, Hurwitz et al. reported that 25-Hydroxy Vitamin D deficiency in hospitalized patients with RSV infection (including human metapneumovirus infection) was associated with a higher risk of requiring ventilator management[8]. However, this study included children under 5 years of age, and reported that vitamin A deficiency was also present in many patients, with a large proportion of them being African-Americans (about 70%). Compared to our study and the study by Beigelman et al., the age range of the subjects was higher, and it is possible that not only 25-Hydroxy Vitamin D but also other nutritional conditions may have affected the results.

More research on 25-Hydroxy Vitamin D deficiency is also required. Wierzejska et al. analyzed maternal and cord blood 25-Hydroxy Vitamin D levels in Poland, and reported that 25-Hydroxy Vitamin D levels were significantly higher in both maternal and cord blood in the summer birth group than in the winter birth group[29]. In our study, 5 patients (cases 11 to 15) who were not 25-Hydroxy Vitamin D deficient were born in April, May, June, and August, but 2 patients (cases 2 and 3) born in June and August had serum 25-Hydroxy Vitamin D levels less than 4 ng/ml. In addition, both the RSV hospitalized group and the control group that we analyzed had low serum 25-Hydroxy Vitamin D levels, and it was hence suspected that many infants hospitalized early after birth have 25-Hydroxy Vitamin D deficiency. Although data on young disease-free infants is unavailable, this may be a trend regarding serum 25-Hydroxy Vitamin D levels in young infants in Japan. A further understanding of the clinical features of 25-Hydroxy Vitamin D deficiency is needed, although it may be affected by maternal nutritional status and UV exposure time.

Further information on the association between 25-Hydroxy Vitamin D and immunity is required. It has been reported that 25-Hydroxy Vitamin D has a non-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100 μg/mL of active vitamin D added
10,000 μg/mL of active vitamin D added
1. IL-8 (CXCL8)
2. IFN-γ
3. TNF-α
4. IL-1β
5. IL-2
6. IL-4
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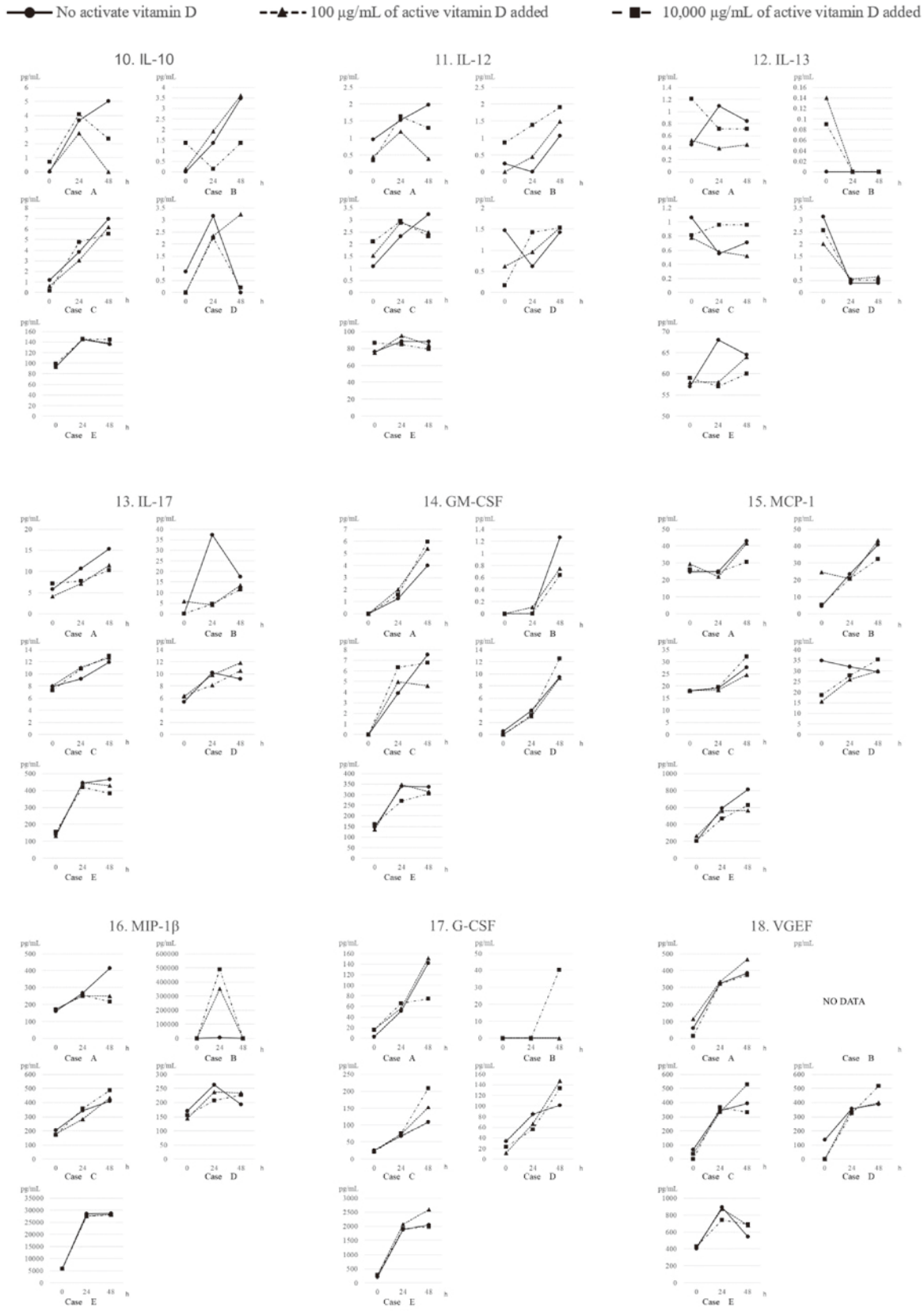
8. IL-6
9. IL-7
pg/mL
Case A
Case B
Case C
Case D
Case E
0 24 48 h


No activate vitamin D
100 μg/mL of active vitamin D added
10,000 μg/mL of active vitamin D added
10. IL-10
11. IL-12
12. IL-13
13. IL-17
14. GM-CSF
15. MCP-1
16. MIP-1β
17. G-CSF
18. VGEF
NO DATA
Case A
Case B
Case C
Case D
Case E

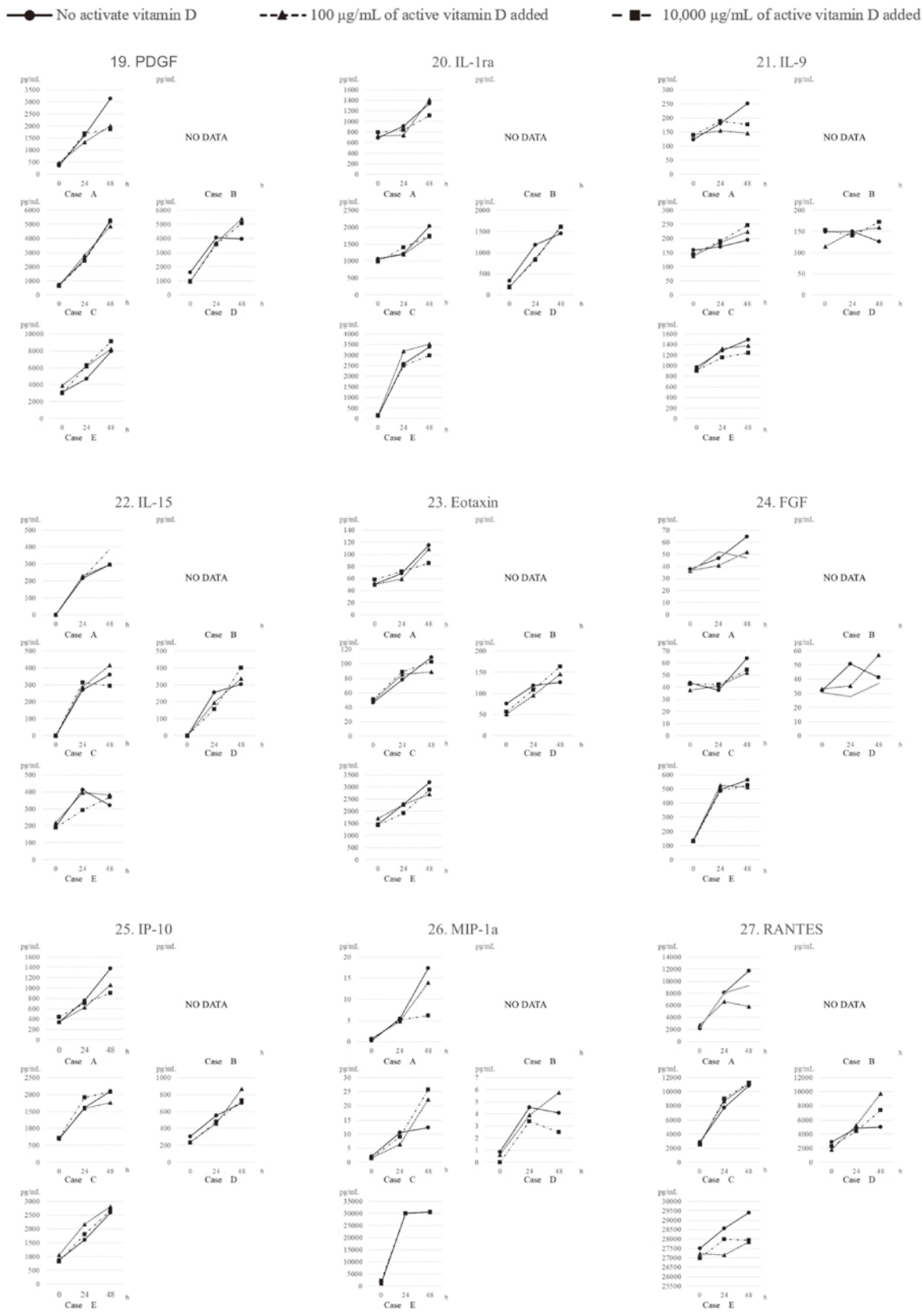


Fig. 2. Cytokines and chemokines produced in peripheral whole blood (200 μL) after the addition of RSV antigen and 25-Hydroxy Vitamin D (0, 24, 48 hours)
IL-8-251A/T in Case C was TT. The other four samples were AT.
The production of IL-8 (No. 1) tended to be suppressed in a 25-Hydroxy Vitamin D concentration-dependent manner in Cases A and B. However, no such trend was observed in the other Cases, nor was there a clear trend by IL-8-251A/T.

genetic effect on innate and acquired immunity[13] and that 25-Hydroxy Vitamin D suppresses major markers of inflammation such as MCP-1, IL-6, and IL-8[15]. On the other hand, in patients with severe RSV infection, the severity of disease has been evaluated by cytokine and chemokine levels, such as high levels of IL-8 production[11]. In the present study, we investigated the effects of 25-Hydroxy Vitamin D on these cytokines and chemokines with the addition of RSV antigen. To the best of our knowledge, similar studies have not been reported to date. Although it still remains unclear owing to the small number of patients that we analyzed, we demonstrated that IL-8 production tends to be suppressed in a 25-Hydroxy Vitamin D concentration-dependent manner in some patients. We believe that this point should be further investigated in the future.

The association between 25-Hydroxy Vitamin D deficiency and RSV infection is thought to be multifactorial. In recent years, genetic predisposition has been attracting attention as one such factor. A British study by Jolliffe et al. including both children and adults reported that a SNP in the 25-Hydroxy Vitamin D receptor (VDR) gene was associated with the risk of upper respiratory tract infection in a discovery cohort and a validation cohort[28].

In addition, studies reporting VDR gene polymorphisms and the risk of lower respiratory tract RSV infection in infants have been reported from Canada and South Africa[31-32]. These studies did not mention much about the association of RSV infection with serum 25-Hydroxy Vitamin D level, and hence whether it is a risk for the development of RSV infection or a risk for severe disease needs to be analyzed. These considerations suggest that there may be a group of people who are at higher risk of developing RSV infection owing to genetic polymorphisms, independent of serum 25-Hydroxy Vitamin D level. Similarly, it has been reported that some genotypes of IL-8 production are associated with higher protein expression and a higher neutrophil chemotaxis index[16-18]. It is hence possible that these factors also affect the severity of RSV infection. Whether 25-Hydroxy Vitamin D has any effect on these factors is not known at present.

In addition, simply having a high serum 25-Hydroxy Vitamin D level may not be enough to prevent severe RSV infections. A systematic review by Limin et al. that included only randomized controlled trials in subjects under 18 years of age reported a lack of evidence that 25-Hydroxy Vitamin D supplementation prevents acute respiratory infections[33].

In conclusion, our study suggests that 25-Hydroxy Vitamin D deficiency alone is not a risk factor for severe RSV infections, similar to previous studies. However, we were unable to assess serum 25-Hydroxy Vitamin D levels in children with spontaneous RSV infection who were being treated as outpatients, which is also similar to previous studies. To pursue the association between 25-Hydroxy Vitamin D deficiency and RSV infection, further clarification of the immunological effects of 25-Hydroxy Vitamin D deficiency, the mechanisms causing severe RSV infection, genetic predisposition, and environmental factors by their simultaneous assessment, including the assessment of spontaneous RSV infections that can be treated as outpatients, is required. Regarding clinical research, larger cohort studies need to be performed. In addition, the immunological effects of 25-Hydroxy Vitamin D on RSV infection severity needs to be further investigated.

Limitations

As this study was conducted only at a single institution and the number of cases was very small, the extent to which it reflects the actual situation remains unclear. In addition, we were not able to analyze serum 25-Hydroxy Vitamin D levels in maternal and cord blood, the ratio of breast milk/artificial milk fed to each patient, whether the patients were taking 25-Hydroxy Vitamin D supplements sunshine exposure hours during the study period, and UV exposure.

Conclusion

25-Hydroxy Vitamin D deficiency can be a risk factor for morbidity of RSV infection, but does not affect the severity of the disease. Further research is needed to investigate the epidemiology of 25-Hydroxy Vitamin D deficiency, the immunological mechanisms by which 25-Hydroxy Vitamin D deficiency affects children with RSV infection, and possible preventive and therapeutic measures.

Conflict of Interest Form

Research funding was provided by Japan Agency for Medical Research and Development (AMED ; grant no. : 20fk0108119h0001).

Abbreviations used

AMED : Japan Agency for Medical Research and Development
DNA : Deoxyribonucleic Acid
FGF : Fibroblast Growth Factor
HFNC : high-flow nasal cannula oxygen
IFN : Interferon
IL- : Interleukin-
IP-10 : Interferon gamma-induced protein 10
G-CSF : Granulocyte Colony Stimulating Factor
GM-CSF : Granulocyte Macrophage Colony-Stimulating Factor
MCP-1 : Monocyte Chemoattractant Protein-1

MIP : Macrophage Inflammatory Protein
NPPV : noninvasive positive pressure ventilation
NT-proBNP : N-terminal pro-natriuretic Peptide
PBMCs : Peripheral Blood Mononuclear Cells
PCR : Polymerase Chain Reaction
PDGF : Platelet-Derived Growth Factor
RANTES : Regulated on Activation Normal T Cell Expressed and Secreted
RFLP : Restriction Fragment Length Polymorphism
RSV : Respiratory Syncytial Virus
SNP : Single Nucleotide Polymorphism
TNF : Tumor Necrosis Factor
VDR : 25-Hydroxy Vitamin D receptor
VEGF : Vascular Endothelial Growth Factor

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Author contributions

GK, as first author, analyzed and interpreted the data and conceived and wrote the paper ; YK performed the experiments and collected the data ; KS and HK provided technical assistance and conceptual advice. All authors read and approved the final manuscript.

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RS ウイルス感染症に罹患した早期乳児における 25-OH ビタミン D 値の意義

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【背景と要旨】
近年、出生時ビタミン D 欠乏症は生後 1 年までの RS ウイルス感染症の罹患率を増加させると報告された。一方で、ビタミン D 欠乏症と RS ウイルス感染症の重症度については見解がない。また、ビタミン D が RS ウイルス感染症に対する免疫反応にどのような影響を及ぼしているかは解明途中である。本研究では東京地区における RS ウイルス感染症で入院した早期乳児の血清 25-OH ビタミン D 値と臨床像を検討した。また、RS ウイルス感染症の重症度に影響を与えうるサイトカイン、ケモカインの産生がビタミン D の添加により変化するかを実験室的研究として追加した。
【方法】
2012 年 11 月から 2021 年 7 月に東京医科大学病院に入院した RS ウイルス感染症の生後 3 か月未満の乳児 15 名を対象とした。対照として、同期間に RS ウイルス感染症以外で入院した生後 3 か月未満の乳児 8 名を対象とした。入院時に血清 25-OH ビタミン D 値を測定し、診療録から臨床的特徴を後方視的に検討した。また、上記とは異なる 5 検体を対象に、RS ウイルス抗原で刺激した末梢全血中から産生されるサイトカイン・ケモカインを活性型ビタミン D 濃度別にそれぞれ分析した。
【結果】
入院時の血清 25-OH ビタミン D 値と RS ウイルス感染症の重症度との間に関連は認められなかった。RS ウイルス感染症で入院した乳児は、対照群に比べ血清 25-OH ビタミン D 濃度が低い傾向にあったが統計学的に有意ではなかった（$p = 0.293$）。実験室的研究では、一部の症例で IL-8 産生がビタミン D 濃度依存性に抑制されたが、明確な結論は導き出せなかった。
【考察・結論】
東京地区における乳児において，ビタミン D 欠乏症のみでは RS ウイルス感染症の重症度に関連していなかったが血清 25-OH ビタミン D 値が低い傾向にあった。交絡因子が多いため、臨床研究のみでは評価に限界がある。RS ウイルス感染症の重症度に影響を与える免疫機構、遺伝的な背景などとビタミン D 欠乏症の関連があるか今後検討していく。

〈キーワード〉 RS ウイルス、早期乳児、ビタミン D