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A case study of IgG3 deficiency regarding the severity of Influenza H1N1 pdm 09

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Running Title

IgG3 deficiency in Influenza H1N1 pdm 09

Key Words:

IgG3 deficiency

asthma

influenza H1N1 pdm 09

pneumonia

admission duration

Abstract

Background: The severity of the 2009 pandemic H1N1 Influenza (H1N1 pdm 09) in the immune deficient children is unknown. We investigated this issue in a case of complete IgG3 deficiency complicated by pneumonia and asthma attack.

Methods: We compared the clinical parameters of the case of IgG3 deficiency with 4 control patients by 95% confidential intervals. These control patients were selected from 71 admitted patients because of pneumonia or bronchitis caused by H1N1 pdm 09 in terms of age, the absence of pretreatment with oseltamivir before admission, the presence of a past history of asthma, the use of antibiotics, and combined inhalation of a beta 2 agonist and intravenous methylprednisolone administration for asthma attack.

Results: The case showed significantly longer duration of admission and period of oseltamivir administration, with a significantly decreased pulse oxygen saturation level and increased maximal values of serum CRP, CK and urinary excretion of beta 2 microglobulin/creatinine for influenza H1N1 pdm 09 admission, compared with the controls($P<0.05$).

Conclusions: These preliminary data suggested the clear influence of complete IgG3 deficiency on the severity of the clinical course of pneumonia and asthma attack in children suffering from the H1N1 pdm 09.

Introduction

The 2009 pandemic H1N1 Influenza (H1N1 pdm 09) was firstly reported in Mexico at the end of March, 2009 (1) and spread all over the world in about 2 months as a new pandemic influenza. With this new influenza infection, a high incidence of respiratory failure patients who needed admission was reported compared to seasonal influenza in many countries including Mexico (2), and the United States of America (3). Especially, it was noted that young people, including small children, were admitted due to pneumonia in the early stage of infections (4). The reason for this was speculated to be the strong invading characteristics of the pandemic influenza virus in the lungs (5). Recently, host adaptive immune deficiency was reported in severe pandemic influenza (6). In fact, Gordon CL et al. (7) reported that severe H1N1 infection was associated with IgG2 deficiency. However, the severity of the H1N1 pdm 09 in children of a subclass with an IgG deficiency is unknown. Here, we report a case of complete IgG3 deficiency complicated by pneumonia and asthma attack caused by the H1N1 pdm 09.

Materials and Methods

A total of 71 Japanese patients (46male, 25female) were admitted to Minoh city hospital suffering from mild pneumonia caused by influenza like illness (ILI) between September 2009 and January 2010 including a case of complete IgG3 deficiency. The

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patient was a 5-year-old boy who had a past history of asthma. He was previously healthy and no history of admission. They all proved to be infected with influenza A by an immunologic rapid test. Diagnosis of influenza A was made by the immunologic rapid test of Espline (Fujirebio, Japan). We measured serum levels of IgG subclasses in 45 out of these patients by a method of nephelometry (BML, Japan). The presence of pneumonia was confirmed by the chest roentgenogram on admission. We treated all patients with anti influenza a neuraminidase inhibitor (oseltamivir or zanamivir) and Mao-to (8). Mao-to is a Japanese traditional herbal medicine, which was reported to be effective against seasonal influenza infection (8). This protocol was approved by the review board of Clinical Ethical Committee of Minoh City Hospital.

Parameters investigated in the above 45 patients were the presence or absence of a more than 38°C fever, cough, nausea/vomiting, SPO₂ levels and the duration from the onset of clinical signs and symptoms of influenza to admission. The latter included the worst clinical data on admission, for example maximal body temperature, respiration and pulse rate, the duration necessary for defervescence below 37.5 °C and the period of oseltamivir administration. We also investigated laboratory data such as blood cell counts of WBC with the percentage of granulocytes, platelet number, biochemical markers including serum CRP, LDH, CK, IgG subclasses (IgG1, IgG2, IgG3 and IgG4)

and urinary beta 2 micro globulin/urinary creatinine values.

We selected 4 clinical controls who were matched to the present case with complete IgG3 deficiency by the age, the absence of pretreatment with a neuraminidase inhibitor before admission, the presence of a past history of asthma, the use of antibiotics either orally or intravenously and therapy for asthma on admission such as inhalation of a beta 2 agonist combined with infusion of methylprednisolone for asthma attack. Then, we calculated 95% CI values for each parameter to compare the corresponding data with the present IgG3 deficiency case. Data were shown as mean values with 95% confidential interval (CI). using JMP 8.02(SAS, Japan)

Results

1. Clinical profiles of a patient with complete IgG3 deficiency

The case was a 5-year-old boy. He visited a family doctor complaining of high fever and severe cough on October 23rd, 2009. Physical examinations revealed retraction with a decreased pulse oxygen saturation (SpO₂) level of 92%. An influenza rapid test was negative. He was the first child of healthy and unrelated parents without a past history of recurrent infectious diseases such as pneumonia or sinusitis. He suffered from asthma

and serum IgE levels were pointed to be elevated (447 UA/ml). He was referred to Minoh city hospital for pneumonia treatment on October 24th. On admission, he was pale and a roentgenogram revealed bilateral pneumonia (Fig 1). Data for the venous gas analyses were as follows; pH 7.376, PCO₂ 31.7mmHg, HCO₃ 18.2mEq/l, BE – 5.7. We gave him a maximal 8L/min oxygen to keep his SpO₂ levels above 95%. On October 25th, an immunologic rapid test for influenza revealed influenza A, which proved to be the H1N1 pdm by PCR. The worst data for WBC and a percentage of granulocytes were 10,700/microl and 95.5% respectively with normal platelet levels. Biochemical markers revealed a maximal CRP value of 6.6 mg/dl with normal levels of LDH, CK, Na and albumin. In contrast, a maximal urinary beta 2 micro globulin/urinary creatinine values were 12,023 microg/gCr (Figure 2). On October 26th, serum levels of IgG, IgM and IgA revealed 718mg/dl, 133mg/dl and 168mg/dl respectively. Serum concentrations of IgG subclasses were as follows; IgG1 : 393mg/dl, IgG2 : 204mg/dl, IgG3 : undetectable(<4)mg/dl and IgG4 : 13mg/dl. The data of IgG1, IgG2 and IgG4 were within normal range according to the corresponding Japanese data (9). No pathological bacteria were isolated from the nasopharyngeal specimen in culture. Also, a rapid test for pneumococcus infection was negative in urine specimen. No bacteria were isolated from blood specimen. We reconfirmed a positive result for an immunologic rapid test

for influenza A on October 29th, however we had no data to prove a prolonged viral shedding thereafter.

On admission, we started to treat him with a combination of a neuraminidase inhibitor (oseltamivir), Japanese herbal medicine (Mao-to) (8), several antibiotics, inhalation of a beta 2 agonist in a continuous nebulized formulation and intravenous administration of methylprednisolone. Following these therapies, body temperature returned to normal within a day, but it took total of 3 days to the normalize respiration rates. Also, we gave him low volume oxygen for a week because of the asthma attack and he had to stay in the hospital for 12 days (Figure 2).

2. A Comparative study between a patient with IgG3 deficiency and clinical controls

Table 1 showed only the statistically significant ($p<0.05$) data of parameters investigated for the clinical signs and symptoms of influenza on admission and the worst clinical data during the hospital stay. They were duration of admission, a SPO_2 level on admission, biochemical markers of CRP, CK values, urinary beta 2 micro globulin/urinary creatinine values, serum concentrations of IgG3 and the period of oseltamivir administration.

Discussion

This study showed for the first time that a complete IgG3 deficiency affected the clinical course of children suffering from H1N1 pdm 09 and pneumonia. Recently, an immunodeficiency was reported as a risk factor of H1N1 pdm 09 (10), however, no reports showed the clinical outcome of children with IgG3 subclass deficiency in H1N1 pdm 09. This was probably because IgG3 subclass deficiency was relatively rare in children compared to adults (11).

Asthma was reported as a risk factor for H1N1 pdm 09 (12). Also, asthma was a complication of the IgG3 subclass deficiency (13). In the present case, the duration of admission, which was a possible hallmark of the severity of H1N1 pdm 09, was significantly longer than that of clinical controls. However, it was difficult for us to indicate that this was caused by asthma because we adjusted it as one of the base line characteristics in our study. In addition, he needed a longer period of oseltamivir administration to treat the influenza compared to the clinical control patients. Thus, these data may be due to the prolonged virus shedding as seen in the other immunocompromised patients in H1N1 pdm 09 (15), although we had no data to prove the hypothesis. On the basis of these data, we postulate that immunodeficiency due to complete IgG3 deficiency clearly affected the severity of the clinical course of children

suffering from pneumonia and asthma caused by H1N1 pdm.

Although the precise mechanism for the above was unclear, two hypotheses are plausible. One is that a condition of immunodeficiency making a patient susceptible to bacterial infections. However, we found no abnormality in culture analyses of blood and upper respiratory swabs. Thus, the former hypothesis was likely to be implausible, although we could not completely exclude the possibility. The other is a decreased immunological defense ability to eradicate the influenza virus from the body. In fact, IgG3 was suggested to be associated with the primary response in the respiratory viral infection (16). In our case, we treated all the patients on admission caused by H1N1 pdm 09 with oseltamivir and Mao-to, a Japanese herbal medicine. The usefulness of this kind of combination therapy was reported in the case of seasonal influenza (8).

We found no abnormality in serum IgG2 levels which was reported by Gordon CL et al. (6). This discrepancy was speculated to be derived from the difference in the clinical severity and age of the patients; the children with pneumonia stayed on a regular floor without mechanical respiratory assistance in a municipal hospital in our case compared to adult patients with severe respiratory failure, who were admitted to the intensive care unit in a center hospital.

The evidence in this report is limited, and it was unclear whether the severity of the

clinical course for pneumonia and asthma attack in this case was derived from H1N1 pdm 09 influenza or influenza it self. Although the patient had no past history of pneumonia caused by seasonal influenza, he was the only case with IgG3 deficiency in our experience. Thus, we could not conclude whether the relatively severe clinical course in this case was caused by H1N1 pdm 09. However, frequency of IgG3 deficiency in children was relatively low (11), and the importance of IgG3 deficiency was recently suggested for recurrent infections (13). Thus, we thought it worthwhile to report our experience and preliminary analyses even in a single case of complete IgG3 deficiency. Further study is necessary to elucidate the mechanism of IgG3 deficiency complicated by pneumonia and asthma attacks in the severity of H1N1 pdm 09.

In conclusion, we showed the possible impact of complete IgG3 deficiency on the severity of the clinical course of pneumonia in children suffering from H1N1 pdm 09.

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Figure Legends

Figure 1

Clinical course

We gave oseltamivir, mao-to, antibiotics and steroid hormone treatment.

Note that he needed high volume oxygen at first and we could not stop low volume oxygen for one week to maintain over 95% SpO2 values.

SpO2: saturation pulse oxymetry., ABPC: aminobengel penicillin.

SBT: sulbactum., AZM: azisuromicine.

CAM:clarithromycine., mPSL:methyl prednisolone.

neut:neutrophil., b2 MG:β beta 2 micro globulin.

Figure 2

Chest roentgenogram

Note the presence of bilateral pneumonia on admission. On the second hospital day,pneumonia in the left side extended to the lower 1/3 area with pleural fluid.

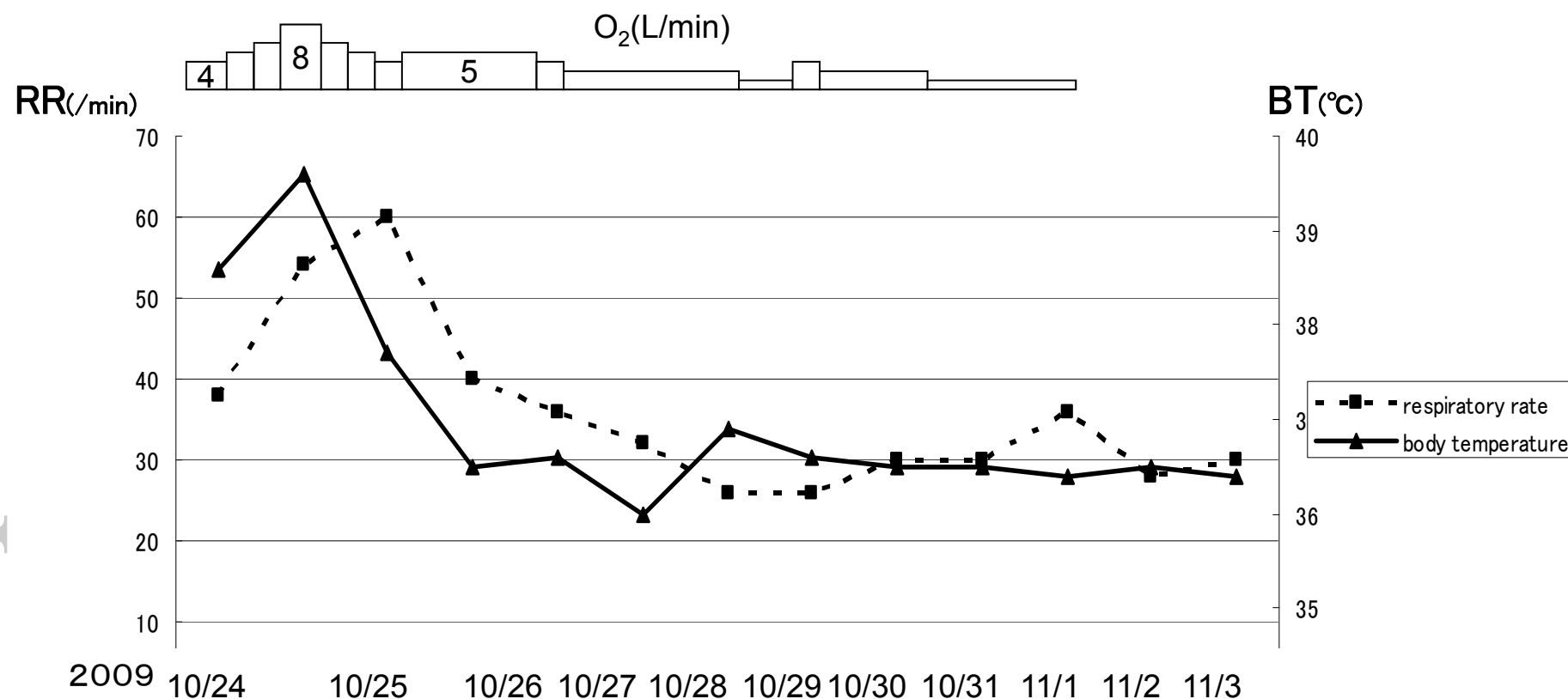
Table 1**Clinical data of a case of IgG3 deficiency compared with clinically matched controls**

Parameters	the present case	control patients (n=4: 95% CI)
IgG3 (mg/dl)	<4	14~39
SPO₂ values on admission (%)	90	92~97
CRP (mg/dl)	6.6	-2.4~6.0
CK (IU/l)	618	57~278
u- beta 2 microglobulin/creatinine value(microg/gCr)	12023	878~4729
duration of oseltamivir administration (days)	10	3.4~8.1
duration of admission(days)	12	6.5 ~10.6

Note: The mean age and 95% values of control patients were 5.5 and 4.2~6.9 years old respectively. Control patients were matched with the present case by age, the absence of pretreatment with oseltamivir before admission, the presence of a past history of asthma, the use of antibiotics, combined inhalation of beta 2 stimulator and intravenous methylprednisolone administration for asthma attack.

Only the parameters with $P < 0.05$ values are shown.

Oseltamivir 4mg/kg/day			
Mao-to 0.2g/kg/day			
ABPC/SBT 150mg/kg/day			
AZM 10mg/kg/day		CAM 5mg/kg/day	
mPSL 1.3mg/kg/day			

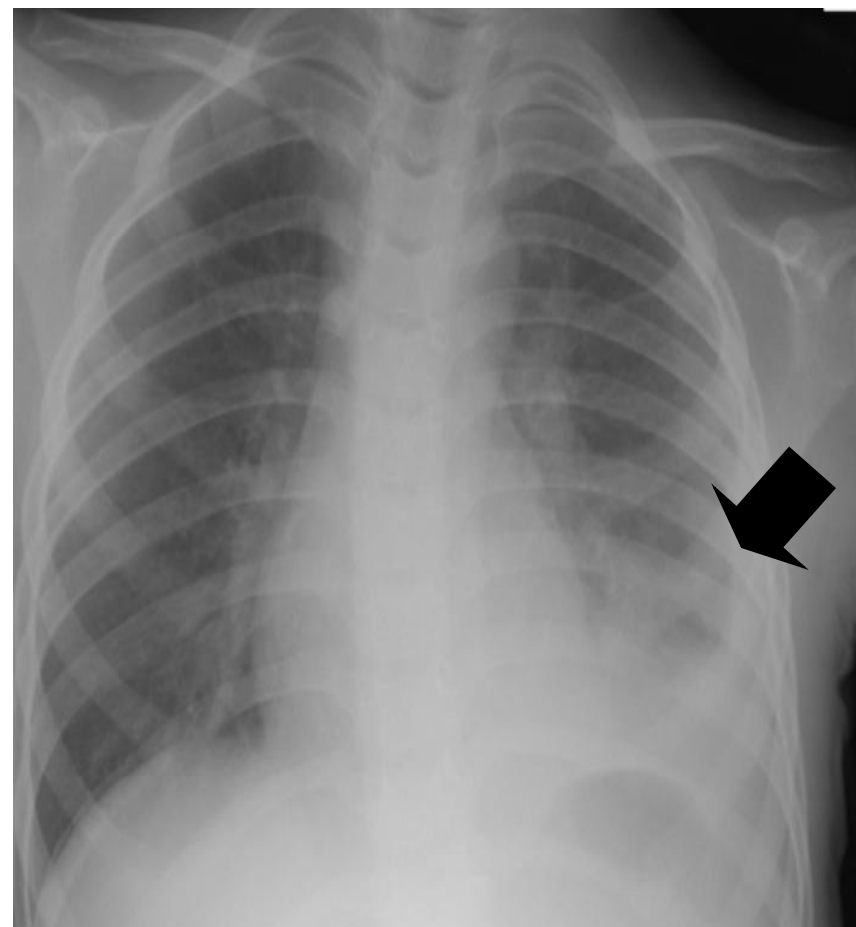


WBC(μl)	7900	9100	10700	10500
Neut(%)			95.5	65.0
CRP(mg/dl)	1.2	6.6	2.6	0.24
U-β2MG/Cre (mg/gCr)		12023	1569	332

Chest Roentgenogram



On admission



On the second hospitalization day