Case Report

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TANAFFOS

Trisomy 21 as a Risk Factor for Severe Illness in COVID-19: Report of two Cases

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COVID-19 leads to mild symptoms within the majority of infected patients, but can cause severe multiple organ failure and death. There is only limited information regarding the consequences of this new emerging infection with congenital disorders. According to the previous studies, many people with Down syndrome are considered high risk for complications related to respiratory diseases.

We report two trisomy 21 patients who suffered from COVID-19 and summarize the early experience with COVID-19 and Down syndrome.

The course of the disease was severe in these two cases, and our concern is close monitoring of the patients with Down syndrome for early signs of COVID-19.

Key words: Down syndrome; COVID-19; Risk factors; Trisomy, Risk factor

INTRODUCTION

Triplication of chromosome 21 causes the conditions commonly referred to as Trisomy 21or Down syndrome (DS). DS is the most frequent chromosomal abnormality in the human population, and also the most common survivable autosomal aneuploidy (1).

Respiratory involvements and cardiovascular diseases are the most common cause of hospital admissions and increasing the mortality rate in patients with Down Syndrome (2). Some related problems such as hypotonia, obstructive sleep apnea, craniofacial anomalies, immune deficiency, cardiac involvements and gastroesophageal reflux (GERD) can increase the risk of respiratory complications including aspiration pneumonia and recurrent pulmonary infection (3,4).

Common clinical manifestations of coronavirus disease 2019 (COVID-19) consist of fever, cough, myalgia, expectoration, dyspnea, headache, dizziness and diarrhea (5). Infected patients may suffer multi-organ failure especially pulmonary and cardiovascular involvements (6). Given the above, we can expect that respiratory diseases in DS are more common than in healthy people who have COVID-19 diseases.

In this paper, we report two patients with trisomy 21 who suffered COVID-19 and discuss the early experience with COVID-19 and DS patients.

CASE SUMMARIES

Case 1

The case I was a 32-year-old female with DS (living in a chronic care facility) who came to our center, Masih Daneshvari Hospital simultaneously as her mom, 4 days after the beginning of the daughter's symptoms and 7 days after mother's. They had dry cough, mild fever, chest pain, and non-exertional dyspnea. At the beginning of the

visit, the daughter's oxygen saturation was about 75% in the ambient air. Imaging studies showed multiple round ground-glass opacities in both lungs especially at lower lobes (Figure 1 A and B). Paraclinical studies have shown that real-time polymerase chain assay (RT- PCR) for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was positive for both of them. Other necessary information is shown in table 1. Oxygen therapy with facemask, administration of antiviral (Lopinavir/ritonavir) and antibiotics (ceftriaxone and azithromycin), as well as naproxen was started. The cardiologist consultation was done and echocardiography was normal. Her general condition was satisfactory and oxygen saturation was around 89 to 91% with supplemental oxygen therapy.

Table 1. Summary of two cases

		Case 1	Case 2
Demographic data	Age	32	34
	Gender	Female	Female
	Time interval between first symptoms to hospital admission	4 days	10 days
	BMI [a]	34.1	38.3
Presenting illness	Fever	Yes	No
	Cough	No	Yes
	myalgia	Yes	Yes
	dyspnea	Yes	Yes
	chest pain	Yes	Yes
	Hemoptysis (non-massive)	Not at first but developed during hospitalization	At the beginning of admission
Laboratory information	WBC [b]	4000	8350
	Neutrophils	65%	81.7%
	lymphocytes	30%	14.9%
	Eosinophils	2%	0.1%
	Hemoglobin	10	14.5
	Platelet	130000	132000
	ESR [c]	5	35
	Fasting blood sugar	96	128
	CRP [d]	26	47
	AST [e]	21.2	45
	ALT [f]	63	17
	LDH [g]	558	1535
	Urea	23	50
	Creatinine	1	1.2
	Ferritin	900	1120
	D-Dimer	400	2560
	Procalcitonin	Negative	Negative
	RT-PCR COVID-19 [h]	Positive	Positive
	Interleukin 6	2	31.6
	Blood culture	No growth	No growth
	Tracheal culture	-	No growth
Treatment	Anti-viral	Lopinavir/ritonavir	Favipiravir
	Antibiotics	Ceftriaxone Azithromycin	Meropenem Vancomycin
	interferon beta 1-alpha	12×10^6 unit 5 doses	12×10^6 unit 2 doses
	IVIG [i]	25 gr, 3 dose	25 gr, 1 dose
	NSAID [j]	Naproxen	-
	Hydroxychloroquine	400 mg stat	400 mg stat
	Corticosteroid	Single-dose /200 mg hydrocortisone -IV	100 mg hydrocortisone IV TDS
Radiological findings	Chest x-ray	bilateral, predominantly peripheral, asymmetrical consolidation	bilateral, generalized, asymmetrical consolidation
	CT scan	multiple round ground glass infiltration	Generalized ground glass infiltration
Intensive care	Admission	24 days	3 days
	Intubation	NO	YES
	NIV [k]	YES	NO
Outcome		Discharged from hospital	Death in hospital three days after admission

[a] Body mass index; [b] White Blood Cell; [c] Erythrocyte Sedimentation Rate; [d] C-Reactive Protein; [e] Aspartate Aminotransferase; [f] Alanine Aminotransferase; [g] Lactate Dehydrogenase; [h] Real-time polymerase chain reaction; [i] Intravenous Immunoglobulin; [j] Non-steroidal Anti-inflammatory Drugs; [k] Non-invasive ventilation

During the hospital stay, she developed streaky hemoptysis, and oxygen saturation was reduced to 70% in the 7th day of admission without response to supplemental oxygen. Therefore, she was referred to the intensive care unit (ICU) and Interferon beta 1-a (with dosage of 12 million units every other day subcutaneously) and IVIG started for her. She was under noninvasive ventilation in the ICU and her condition improved gradually. After 3 days, she came back to the infectious disease ward, and after 10 days discharged.

Her mother was a 63-year-old woman with no underlying disease and her symptoms were very mild, although she had an almost moderate involvement in computed tomography (CT) scans.

We performed flowcytometric study for this patient which summarized in table 2. Recovery T-cell response were seen in sequential analysis of cellular immunity response.

Table 2. Flowcytometric analysis of case I

Day from symptoms onset	(7th day)		(13th day)		(17th day)	
Disease severity*	Severe		Critical		moderate	
WBC	3580		4410		5310	
Total lymphocyte	31% (1110)		33.2% (1464)		33.1% (1758)	
CD_3+	80	888	74	1083	76	1336
CD_4+	53.7	596	58.7	859	52	914
CD_8+	25	277	19.7	288	24	422
CD_4+/CD_8+ ratio	2.15		3		2.2	
$CD_{16\text{-}56}$+	13.8	153	18.3	268	14.6	1758
CD_{19}+	3.9	43	6.5	95	4.5	79
CD_{20}+	4	44	5.6	83	4.27	75
CD_{27}+	10	111	11.4	167	11.4	200
CD_{38}+	9.37	104	11.1	162	29.2	513
CD_3+HLA DR+	5.37	60	15.9	233	16.5	290

* Moderate is defined as O_2sat≥93 in ambient air; Severe is defined as O_2sat<93 in ambient air; Critical is defined as refractory hypoxemia needs admission in the critical care unit.

For every subset, the first column is the percentage of total lymphocyte and the second column is absolute count (per/µl).

Case 2

Case II was a 34-year-old female with DS (living in with her family) who came to our center ten days after her symptoms began. He had cough, shortness of breath, fever, myalgia, and hemoptysis. At the time of arrival to the hospital, oxygen saturation was about 69% in the room air without respiratory distress. In chest X-ray and pulmonary spiral CT scans, generalized ground-glass opacification was seen in both lungs (Figure 1, C and D).

Her sample from oropharyngeal gargling was positive for SARS-CoV-2 by RT-PCR assay. Other necessary information is shown in table 1.

With supplemental oxygen, O_2 saturation increased to about 86%, but about eleven hours after being hospitalized in the infectious ward, her blood oxygen saturation dropped (to 55%) and developed respiratory distress. We found out that she had suffered from acute respiratory distress syndrome (ARDS) and immediately transferred to the ICU. She was intubated and was treated by antiviral (favipiravir), antibiotics (meropenem and vancomycin), Interferon beta 1-a, IVIG and hydrocortisone, but unfortunately she died three days later despite all efforts.

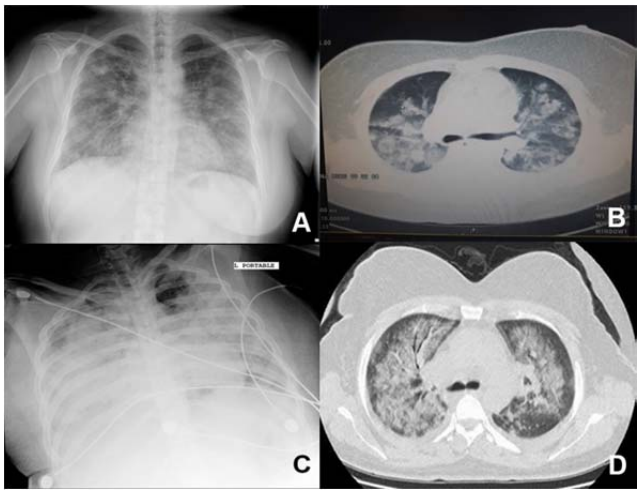

Figure 1. Imaging studies of two DS cases complicated by COVID-19
A and B: The imaging study of case I; C and D: The imaging study of case II

DISCUSSION

In this report, we describe two cases of "Down syndrome" who were admitted to Masih Daneshvari Hospital due to COVID-19 pneumonia. Both had early symptoms such as fever, chest pain, and myalgia, and then entered the acute respiratory distress phase and were admitted to the ICU. One of them, who had risk factors consisting of obesity, coming late for the hospitalization, severe symptoms like hemoptysis, and signals of cytokine storm (such as high levels of CRP and interleukin-6)

unfortunately died. Another case that had better care and came to the hospital earlier saved by receiving the similar treatment (Antivirals, antibiotics, interferon beta, and IVIG) and care in the ICU (7).

DS is the most prevalent chromosomal abnormality that occurs in one per 800 live births (8). Between 1979 and 2003, cases of Down syndrome increased by about 30% (9). Down syndrome can increase susceptibility to infections by altering humoral and/or cellular immunity. So higher rates of hospitalization related to the illness from viral lung diseases, such as respiratory syncytial virus and H_1N_1 influenza A were reported among them (10,11). Pulmonary infection, congenital heart defects and circulatory diseases are responsible for about 75 percentages of all deaths in patients with DS (2).

After emerging the global pandemic of COVID-19 caused by SARS-CoV-2, there are some hypotheses that individuals with DS may experience severe forms of SARS-CoV-2 infections, or may have poorer outcomes in comparison to others (12). This concept originates from the findings of widespread immune dysregulation and the combination of other potential risk factors that are common among the population with DS. For example congenital heart defects as a frequent problem in DS may be a risk factor for severe COVID-19 (13).

Chronic immune dysregulation consisting of a higher prevalence of autoimmune disorders and hospitalization due to respiratory viral infections and bacterial pneumonia are observed among cases with DS. The hyperactivity of interferon (IFN) and increased levels of cytokines in DS patients are more significant than normal population and exacerbated cytokine release syndrome may occur in this condition (12). Cytokine storm is a basic pathology related to the mortality of severe viral infections. In COVID-19, the cytokine storm may lead to shock, tissue damage, acute respiratory distress syndrome (ARDS), multi-organ failure, and finally death (14-17).

T cell lineages of adults with DS reveal apparent conditions of differentiation and hyperactivation, with any infections, which could be clarified by chronic IFN hyperactivity and the presence of high expression of IFN genes. Therefore, effector CD_4 and CD_8 T cells with trisomy 21 are resistant to Treg regulatory T cells (Tregs) function (18).

Tuttle et al. reported results obtained from a mouse model of DS. They demonstrated that these animals overexpress interferon receptor genes (IFNRs) and challenge with a viral mimetic that activates Toll-like receptor signaling and IFN anti-viral response, led to cytokine storm and death among them. A JAK1-specific inhibitor blocked this phenomenon. Therefore, these results point to JAK1 inhibition as a potential strategy for the treatment of the cytokine storm. The presence of an extra copy of the IFNR gene cluster encoded on chromosome 21 in patients with Down syndrome may increase the risk of the disease in these patients during COVID-19 pandemic (19).

CONCLUSION

DS is associated with some problems, such as a weaker immune system, and a greater likelihood of involvement of the respiratory and cardiovascular systems after a viral or bacterial infection.

Regarding to T cell dysregulation associated with IFN hyperactivity, COVID-19 by creating a cytokine storm and adding to the immune system defects in patients with Down syndrome may worsen the condition and increases the risk of death. For this reason, it may be prudent to recommend that patients with Down syndrome be more closely monitored for early signs of COVID-19 especially who had other risk factors for this infection.

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