

## Case Report



# COVID-19 in a 16-Year-Old Adolescent With Mucopolysaccharidosis Type II: Case Report and Review of Literature

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) in patients with underlying diseases, is associated with high infection and mortality rates, which may result in acute respiratory distress syndrome and death. Mucopolysaccharidosis (MPS) type II is a progressive metabolic disorder that stems from cellular accumulation of the glycosaminoglycans, heparan, and dermatan sulfate. Upper and lower airway obstruction and restrictive pulmonary diseases are common complaints of patients with MPS, and respiratory infections of bacterial or viral origin could result in fatal outcomes. We report a case of COVID-19 in a 16-year-old adolescent with MPS type II, who had been treated with idursulfase since 5 years of age. Prior to infection, the patient's clinical history included developmental delays, abdominal distension, snoring, and facial dysmorphism. His primary complaints at the time of admission included rhinorrhea, cough, and sputum without fever or increased oxygen demand. His heart rate, respiratory rate, and oxygen saturation were within the normal biological reference intervals, and chest radiography revealed no signs of pneumonia. Consequently, supportive therapy and quarantine were recommended. The patient experienced an uneventful course of COVID-19 despite underlying MPS type II, which may be the result of an unfavorable host cell environment and changes in expression patterns of proteins involved in interactions with viral proteins. Moreover, elevated serum heparan sulfate in patients with MPS may compete with cell surface heparan sulfate, which is essential for successful interaction between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein and the host cell surface, thereby protecting against intracellular penetration by SARS-CoV-2.

**Keywords:** COVID-19; Mucopolysaccharidosis II; Heparan sulfate

## INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is prevalent worldwide and poses a serious threat to human life. Disease manifestations range from being asymptomatic to presenting with acute respiratory distress syndrome.<sup>1)</sup> While young or previously healthy COVID-19 patients tend to follow an uneventful disease course, elderly patients or those with underlying medical conditions are more likely to require hospitalization and intensive care, including invasive mechanical ventilation, occasionally with fatal outcomes.<sup>2)</sup>

**Author Contributions**

Conceptualization: Park SY, Kang S; Data curation: Chu MA, Chung MH; Investigation: Park SY, Kang S; Methodology: Chu MA; Supervision: Kim HS, Chung MH; Writing - original draft: Park SY, Kang S; Writing - review & editing: Kim HS, Chu MA, Chung MH, Kang S.

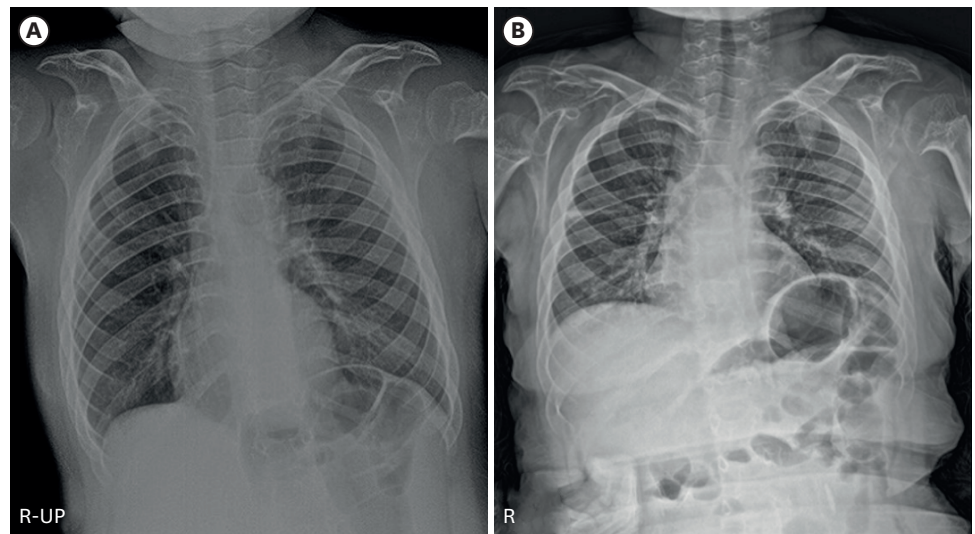
Mucopolysaccharidosis (MPS) type II, also referred to as Hunter syndrome, is a lysosomal storage disease caused by the lack of a specific lysosomal enzyme that degrades glycosaminoglycans. The consequent intra-lysosomal accumulation of heparan and dermatan sulfate in various organs results in progressive cellular damage,<sup>3)</sup> with broad-spectrum chronic, progressive, and life-threatening manifestations.<sup>4)</sup> Respiratory manifestations are a representative symptom of MPS, and common complaints include upper and lower airway obstructions and restrictive pulmonary disease. Bacterial or viral infections that target the respiratory system can consequently lead to fatal outcomes in such patients.<sup>5)</sup> The present study reports COVID-19 in a patient with MPS type II, who displayed minimal symptoms and had a favorable disease outcome. This retrospective analysis was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Hospital (IRB No. 2021-11-074), which waived the requirement for obtaining informed consent from the patient.

**CASE**

A 16-year-old male patient with MPS type II presented with complaints of chills, cough, runny nose, sputum, and loss of appetite. He tested positive for SARS-CoV-2 by real-time polymerase chain reaction (E gene: cycle threshold [Ct] 24.01, RdRP gene: Ct 25.39, N gene: Ct 26.47) and was diagnosed with COVID-19 after being in close contact with his mother, who was infected during a local church outbreak.

The patient was suspected to be a case of MPS at 4 years of age, during a visit to a tertiary hospital in Seoul, Korea, where he had presented with coarse facies, abdominal distension, joint stiffness, hyperactivity, and slurred speech. A diagnosis of MPS II was confirmed by a significantly low leukocyte iduronate-2-sulphatase activity of 0.3 pmol/min/mg protein (normal range, 11–88; affected range, <2.5), and the detection of IDS-IDS2 gene recombination which is diagnostic for MPS type II by polymerase chain reaction-restriction fragment length polymorphism. The patient was subsequently treated with intravenous administration of idursulfase (0.5 mg/kg) once a week from the age of 5. With continuous enzyme replacement therapy, he retained the ability to walk with support, sit and eat regular meals with assistance, and had eventually gained sufficient functionality to attend a special high school. He had learnt to speak by the age of 7, but subsequently lost the ability and currently communicates by turning his face, pulling people, or using simple gestures. In spite of having a tendency to snore, the patient was able to breathe normally without oxygen support or mechanical help. Additionally, while he did not display any signs of sleep apnea, the same could not be confirmed by polysomnography, since he did not undergo the test. The most recent 2-dimensional (2D) echocardiogram recorded at 11 years of age revealed mild aortic thickening, minimal aortic regurgitation, and stenosis, but with good left ventricular function and size.

Post diagnosis with COVID-19, he was admitted to the hospital in charge of COVID-19 patients in the area of his residence. As per the national quarantine guidelines, all patients diagnosed with COVID-19 were to be admitted to the hospital regardless of disease severity, which enabled us to observe his symptoms and vital signs, and have access to his laboratory and radiographic findings during hospitalization. Although the patient had a large tongue, high secretion levels, and chest deformities as manifestations of MPS, he did not complain of breathing difficulties at the time of admission. His height, weight, and head circumference were 131 cm (−6.9 standard deviation score [SDS]), 35 kg (−4.1 SDS), and 57 cm, respectively.



**Fig. 1.** Chest radiographic findings of the patient before and after admission. (A) Chest radiograph performed 3 years before hospitalization. (B) Chest radiograph performed on the day of admission: The image shows no significant changes in comparison to the findings in (A).

His body temperature was 36.9°C, pulse rate was 88 beats/min, respiratory rate was 22 breaths/min, and oxygen saturation was 99%. Chest radiography performed at the time of admission (**Fig. 1B**) revealed no significant changes in comparison to the last most recently recorded at 13 years of age (**Fig. 1A**). Laboratory tests performed on the day of admission showed no abnormal findings except for mild lymphopenia (white blood cell count,  $2.55 \times 10^3/\mu\text{L}$ ; reference value,  $4\text{--}10 \times 10^3/\mu\text{L}$ ), a common finding in COVID-19 patients,<sup>6</sup> and mild anemia (hemoglobin, 11.6 g/dL; reference value, 13.5–17.5 g/dL) that had been persisted from before admission. Aspartate aminotransferase (24 IU/L; reference value, 5–44 IU/L), alanine aminotransferase (16 IU/L; reference value, 5–44 IU/L), blood urea nitrogen (11.8 mg/dL; reference value, 8–20 mg/dL), serum creatinine (0.6 mg/dL; reference value, 0.6–1.2 mg/dL), C-reactive protein (CRP, 0.25 mg/dL; reference value, 0–0.3 mg/dL), and procalcitonin ( $<0.12$  ng/mL; reference value,  $<0.12$  ng/mL) levels were within their normal biological reference intervals.

At hospital day (HD) 6, the patient continued to display symptoms of upper respiratory tract infection without an increase in oxygen demand or respiratory rate. Blood tests revealed recovery of the white blood cell count ( $4.29 \times 10^3/\mu\text{L}$ ), and follow-up chest radiography showed no definite changes in comparison to those recorded in the previous radiographic examination. Chest computed tomography could not be performed on account of the patient's chest deformities and the risk of sedatives such as respiratory depression and was not necessitated since he had mild symptoms with no evidence of pneumonia as seen by the chest radiographic findings. The patient successfully received an intravenous infusion of idursulfase on HD 6 without any complaints, such as urticaria or dyspnea during the procedure.

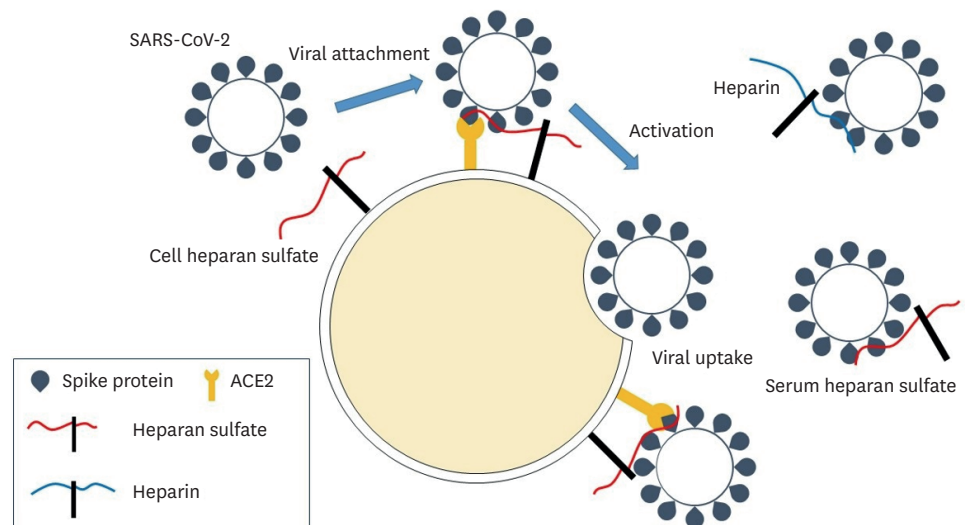
The patient's clinical symptoms, including cough and rhinorrhea receded, and he reported an improvement in appetite by HD 11. He was discharged after 10 days of quarantine and was confirmed to have recovered by 2 consecutive polymerase chain reaction tests for SARS-CoV-2. Further, he had not required treatment with empirical antibiotics, steroids, or antiviral agents during hospitalization. Post discharge, he was monitored regularly and continued to receive intravenous idursulfase infusions once a week at the hospital that he originally attended.

## DISCUSSION

In our study, we report COVID-19 infection in a patient with MPS type II with good clinical outcome. Respiratory involvement is a common finding in patients with MPS, and includes chronic sinusitis, chronic ear infections, recurrent upper and lower respiratory tract infections, and respiratory failure due to airway obstruction by an enlarged tongue, thickened soft tissues, excessive secretions, chest deformities, and spinal instability. Respiratory involvement may further induce obstructive sleep apnea, nocturnal hypoventilation, daytime hypoventilation, and eventually cardiorespiratory failure in these patients.<sup>7)</sup> In spite of a large tongue, high secretion levels, and chest deformities, he had no symptoms of sleep apnea and demonstrated good left ventricular function on 2D echocardiography. This suggests that his cardiopulmonary function was relatively preserved, which may have been partly responsible for the favorable outcome when he contracted COVID-19.

In concordance with our case findings, a few reports state that patients with other lysosomal storage diseases, including Gaucher and Fabry diseases, recover well from COVID-19. Zimran et al.<sup>8)</sup> reported a case of confirmed COVID-19 in a patient with Gaucher disease, who experienced a mild and short clinical course that was managed by quarantine for 14 days. The accumulation of glycosphingolipids in spleen, liver, bone marrow, and lung macrophages of patients with Gaucher disease may promote immune tolerance as opposed to inflammation on exposure to SARS-CoV-2.<sup>9)</sup> Fdil et al.<sup>10)</sup> reported a similar scenario in a 21-year-old male patient who was severely affected by Fabry disease on account of being unable to receive enzyme replacement therapy due to the associated high cost and was diagnosed with COVID-19. Despite his condition, he was asymptomatic for COVID-19 and was managed with home quarantine for 14 days. Ballout et al.<sup>11)</sup> proposed that intracellular biochemical abnormalities that are inherent to lysosomal storage diseases in general, and Niemann-Pick disease type C, in particular, may pose an “unfavorable” host cell environment that impedes the entry, trafficking, and fusion of SARS-CoV-2 with the host cell.

A second hypothesis suggests that the increased tolerance of patients with MPS to COVID-19 is mediated by significant alterations in intracellular gene expression patterns as compared to that in healthy individuals. Pierzynowska et al.<sup>12)</sup> reported that changes in the expression profiles of genes that encode proteins which are present in patients with most types of MPS, and interact with viral proteins, may potentially protect against SARS-CoV-2 infection. For instance, the expression of 4 genes, namely *GTF2F2*, *RAB18*, *TMEM97*, and *PDE4DIP* was downregulated, whereas that of *FBN1* and *MFGES8* was upregulated in nearly all MPS cell types as compared to that in control cells. Of these, *GTF2F2* codes for the general transcription factor IIF subunit 2, known as TFIIF<sup>13)</sup>; which is likely to participate in positive control of viral gene expression. *RAB18* codes for Ras-related small GTPases that are involved in regulation of membrane trafficking and vesicular transport.<sup>14)</sup> *TMEM97* encodes a transmembrane protein that regulates cholesterol levels,<sup>15)</sup> and *PDE4DIP* codes for the phosphodiesterase 4D-interacting protein that is involved in Golgi apparatus function.<sup>16)</sup> While *GTF2F2*, *RAB18*, *TMEM97*, and *PDE4DIP* products are related to efficient infection of host cells by COVID-19, *FBN1* and *MFGES8* are known to be involved in glucose homeostasis and phagocytosis of apoptotic cells, respectively. Further, ACE2 and TMPRSS2 are known to play crucial roles in viral adsorption and intracellular penetration. The transcriptomic analysis revealed that the expression of ACE2 is negligible in all MPS cell lines, except for MPS IVA and VI, in comparison to the low mRNA levels detected in control cells. The expression levels of TMPRSS2 were downregulated in MPS I, II, and IIIB fibroblasts but upregulated in other MPS



**Fig. 2.** Heparan sulfate may be an essential host attachment factor that facilitates SARS-CoV-2 infection through binding to the SARS-CoV-2 spike protein. Heparin inhibits SARS-CoV-2 infection by competing with heparan sulfate for binding with the SARS-CoV-2 spike protein. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

cell types in comparison to that in control cells. These findings suggest the existence of an inherent protective mechanism against COVID-19 in patients with MPS, especially in those with MPS type II.

Heparan sulfate may be an essential host attachment factor that facilitates SARS-CoV-2 infection in various target cells,<sup>17)</sup> by virtue of its highly negatively charged linear polysaccharide moiety, that binds to the receptor binding domain of the SARS-CoV-2 spike protein composed of positively charged amino acid residues.<sup>18)</sup> Heparin, which also carries a negative charge, inhibits SARS-CoV-2 infection by competing with heparan sulfate for binding with the SARS-CoV-2 spike protein. We, therefore, speculate that elevated plasma heparan sulfate in MPS I, II, III, and VII patients<sup>19)</sup> competes for binding to the receptor binding domain of SARS-CoV-2 spike protein with cell surface heparan sulfate, in a manner similar to heparin (**Fig. 2**).

In conclusion, patients with MPS may experience a mild course of COVID-19, unlike that in patients with distinct underlying medical conditions. However, close attention must be paid to clinical course of infection and additional studies in a larger number of cases are essential for proper validation.

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## 요약

코로나바이러스감염증-19 (COVID-19)의 임상 양상은 무증상부터 급성 호흡곤란 증후군에 이르기까지 다양하다. 점액 다당류증(mucopolysaccharidosis) 2형은 글라이코사미노글라이칸(glycosaminoglycan)의 일종인 헤파란 황산염(heparan sulfate)과 더마탄 황산염(dermatan sulfate)의 분해를 촉매하는 효소 결핍에 의해 상기 물질이 리소좀(lysosome)에 축적되는 질환으로 전신 침범, 특히 호흡기침범을 특징으로 한다. 따라서 박테리아나 바이러스에 의한 호흡기 감염은 예후에 치명적일 수 있다. 현재 점액 다당류증 환자에서 제 2형 중증급성호흡기증후군 코로나 바이러스(SARS-CoV-2) 감염 후의 임상 양상에 대한 보고는 매우 드물고, 이에 점액 다당류증 2형으로 효소대체요법을 받고 있던 환자에서 상기 바이러스 감염 후의 임상 양상에 대해 보고하고 관련 문헌에 대해 고찰하고자 한다. 16세 남아로 가족간 전파로 코로나바이러스감염증이 발생하였다. 콧물, 기침, 가래 등 호흡기 증상이 관찰되었다. 발열이나 산소요구도 증가는 없었으며 심박수, 호흡수, 산소 포화도는 정상 범위였고 혈액검사결과에서 백혈구 감소증이 관찰되었다. 흉부 방사선 사진에서 폐렴 소견은 보이지 않았다. 보존적 치료와 격리만으로 증상이 호전되었다. 경미한 임상 양상의 원인으로 전구 물질의 축적으로 인해 바이러스에게 불리한 숙주의 세포 환경, 바이러스와의 상호작용에 관여하는 단백질을 암호화하는 유전자 발현의 특정방향으로의 변화가 제시되고 있다. 또한 점액 다당류증 환자에서 증가된 혈청 헤파란 황산염이 SARS-CoV-2 스파이크 단백질과 숙주 세포의 상호작용에 필수적인 세포 표면의 헤파란 황산염과 경쟁하여 SARS-CoV-2의 세포 내 침투로부터 보호한다는 가설도 있다. 향후 더 많은 사례를 통해 점액 다당류증 등의 리소좀 축적질환에서 코로나바이러스감염증의 발현 양상에 대한 연구가 필요하다.