



Management of COVID-19 pneumonia in a child with NEMO deficiency

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Introduction

X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by hypomorphic mutations in encoding the nuclear factor κ B (NF- κ B) essential modulator (NEMO) protein. This primary immunodeficiency disease is characterized by T and B cell dysfunction, antibody deficiency (hypogammaglobulinemia and hyperimmunoglobulin M), low natural killer cell function, and the impairment of encoding cytokines and chemokines. [1] Patients with NEMO deficiency, susceptibility to bacterial, viral, atypical mycobacterial, and *Pneumocystis jirovecii* infections are well defined. [2]

Coronavirus disease 2019 (COVID-19) is mostly responsible for mild symptoms in children. [3] In a retrospective international cohort, patients with antibody deficiencies are reported as the predominant group with COVID-19, and 20% of patients had combined immune deficiencies or impaired innate immunity. [3]

We aimed to describe the clinical findings, treatment, and outcomes regarding COVID-19 in a child with NEMO deficiency.

Case report

A 6.5-year-old boy with NEMO deficiency was admitted with fever, cough, and diarrhea for 3 days. Five days prior to admission, he was diagnosed with COVID-19 via polymerase chain reaction (PCR) during a contact history screening. Using whole-exome sequencing, X-linked disease-causing

IKBKG mutation (c.1167dupC, E390fsX5) was identified. [4] Hematopoietic stem cell transplantation (HSCT) was performed at the age of 9 months. He achieved a donor chimerism of 96% at month + 10 of HSCT, but this value decreased to 40% after 4 years. He was stable after HSCT with intravenous immunoglobulin (IVIG) replacement and antibiotic prophylaxis. [5]

On admission, his temperature was 38.3 °C, pulse rate was 130 beats/min, respiratory rate was 50 breaths/min, and oxygen saturation was 88% in ambient air. Tachypnea, dyspnea, and rales were detected in the lower left lobe. During the hospitalization period, no system involvement other than the pulmonary system was observed. The laboratory data were as follows: white blood cells count 5.300/mm³ (neutrophils 43.7%, lymphocytes 49%), hemoglobin 9.4 g/dL, platelets 261.000/mm³, erythrocyte sedimentation rate 104 mm/h, C-reactive protein 6.4 mg/dL, and interleukin-6 (IL-6) 48 pg/mL. A chest X-ray showed opacity of the lower left lung. Oxygen support and broad-spectrum antibiotics (meropenem and teicoplanin) were started. Thorax tomography showed bilateral ground-glass opacity and consolidation in the left lower lobe (Fig. 1a, b) compatible with COVID-19 pneumonia. Then, azithromycin, hydroxychloroquine (HCQ), and favipiravir were given, with the permission of the parents. High-dose IVIG (2 gr/kg/dose) was given. Because of progressive respiratory distress, COVID-19 convalescent plasma (15 cc/kg/dose) was given without any adverse events on days 1, 3, and 6 of hospitalization. During follow-up, the tachypnea regressed, and oxygen saturation returned to normal. Lung infiltrations were resolved completely on days 10, and the patient was discharged without any complications.

Discussion

Symptomatic adults infected with SARS-CoV-2 typically present with symptoms of fever, dyspnea, cough, fatigue, and sore throat, while fewer cardiovascular, renal, hepatic, gastrointestinal, ocular, dermatologic, and neurological symptoms are observed. [6] The vast majority of healthy children experience

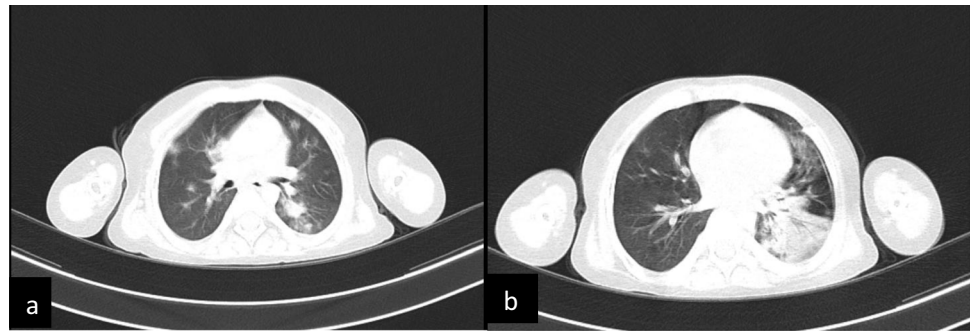
Article Summary: NF- κ B seems an important role in outcome of COVID-19. Here, we discussed COVID-19 pneumonia in a child with NEMO deficiency.

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Fig. 1 Thoracic tomography imaging: Bilateral mild ground glass opacities and consolidation in the left lower lobe



COVID-19 are asymptomatic. In symptomatic patients, fever and cough are the most common clinical manifestations, as well as other signs of viral upper respiratory tract infection; specifically, vomiting and diarrhea can be seen. [7]

The pathogenesis of COVID-19 is not yet clearly understood, but there is evidence of a hyper-inflammatory immune response associated with fatality due to COVID-19. [8] Transcription factor NF- κ B is a master regulator of proinflammatory responses. NF- κ B, in the macrophages of the lung, liver, kidney, central nervous system, gastrointestinal system, and cardiovascular system, triggers the production of various cytokines (IL-1, IL-2, IL-6, IL-12, TNF- α , LT- α , LT- β , and GM-CSF). Hariharan et al. [8] reported that the NF- κ B pathway seems to play an important role in the natural progression of COVID-19. Human hypomorphic NEMO mutations cause diverse clinical phenotypes, infectious susceptibility, and immune capacity. Hanson et al. defined 32 mutations in 72 patients with NEMO deficiency. [9] However, susceptibility to viral diseases was reported in half of patients with NEMO mutations like that observed in our patient. This dysregulated immune response, which is thought to be one of the triggers of the severe form of COVID-19, seems to be related to an initial defect in prompt viral clearance.

B cell deficiency is believed to be protective against the development of inflammation. However, profound systemic inflammatory responses have been observed in adult patients with antibody-deficiency during COVID-19. [10, 11] Because eleven patients with CVID had mild disease, Meyts et al. claimed that adaptive immunity not essential for controlling COVID-19 and that deficient adaptive immune system may even contribute to a milder course by reducing the immune-mediated sequelae. However, nearly half of died patients were CVID, but these patients were older and had comorbidities. [3]

Published data on immunocompromised patients with COVID-19 are very limited. Sixteen adult patients with PIDs (nine patients had CVID, three had X-linked agammaglobulinemia, and one of each had hypogammaglobulinemia, IgA-IgG2 deficiency, IFN-gamma receptor 2 deficiency [IFNGR2], and X-linked hyper-IgM syndrome [XHIGM]) were reported by Ho et al. [11] Pulmonary involvement was seen in thirteen of these patients. Fourteen patients were given HCQ, azithromycin, convalescent plasma (CP), and steroids in various combinations.

Two CVID patient who had NF- κ B subunit 1 mutation recovered quickly. NF- κ B1 is one of the families of inducible transcription factors that regulate the immune and inflammatory responses. The patients had no severe inflammatory response. Meyts et al. recently reported 94 patients, 32 of whom were children, with genetic errors related to immunity and COVID-19. [3] Most of these children had combined immunodeficiency, immune dysregulation disorders, and antibody deficiency (eleven, six, and four patients, respectively). Six patients, including one with NF- κ B2 mutation, required intensive care. One of those with phagocyte defects and those with immune dysregulation died. [3]

Both cellular and humoral immune abnormalities are seen in NEMO deficiency. Hypogammaglobulinemia and specific antibody deficiency generally were reported in patients. Even viral reactivation (EBV, CMV, HSV, and adenovirus) was observed in three patients with NEMO deficiency, despite donor chimerism of 100% and IVIG replacement. [10] In our patient with poor immune reconstruction (40% chimerism), lymphopenia, which associated with disease severity in patients without PIDs, [12] did not develop.

There is no proven treatment regimen for the management of COVID-19 patients. The effectiveness of antiviral drugs, such as remdesivir, favipiravir, lopinavir/ritonavir, and other drugs, such as HCQ, remains controversial even in adult patients. [12] The main approach in children with COVID-19 is supportive therapy. Data about the management of SARS-CoV-2 infection in children with PIDs are even more limited. An 8-year-old boy with specific antibody deficiency exhibited mild symptoms of COVID-19 and then improved rapidly with antibiotics and HCQ. [13].

The COVID-19-specific IgG antibodies in CP are believed to neutralize viral particles, lead to viral elimination, activate the complement system, improve oxygenation, and reduce inflammation. [14, 15] Although its safety and effectiveness have not been evaluated in pediatric patients, it has been used successfully in four children with COVID-19 and acute respiratory distress syndrome. [16] Libster found that the early administration of high-titer CP to mildly ill infected adults was protective against severe COVID-19. Unfortunately, we could not measure the antibody titer of CP. [17]

Ho et al. [11] reported that four of 16 adult patient who had pre-existing PID-associated or other comorbidities died, while two patients with CVID recovered without any therapy. Serum SARS-CoV-2-specific IgG was detected in three patients (two patients had CVID, and one had IFNGR2), and serum SARS-CoV-2 spike protein-specific IgM was detected in one XHIGM, while the other patients were not tested. These CVID patients not required hospitalization. Only one was treated with HCQ and azithromycin. The other two patients were hospitalized but recovered with only steroids and supportive therapy. Four patients with antibody deficiency who received CP recovered. [11] In Meyts et al.'s study, therapeutic medications in children mainly consisted of antibiotics (37.5%) and IVIG replacement (21.8%), while HCQ, systemic steroids, tocilizumab, and antivirals (lopinavir/ritonavir and remdesivir) were used rarely. Two patients with antibody deficiency (*NF-κB2/BTK*) were treated with antibiotics, remdesivir, and CP. [3] The results suggest that a specific antibody response is associated with good outcomes.

Our study has several limitations. We could not measure of antibody titer in plasma and patient serum before and after the treatment.

There is no standard treatment for COVID-19 in patients with PIDs or in healthy persons. COVID-19 disease is usually mild in children. However, as in other infectious diseases, COVID-19 disease can be severe in immunocompromised children, depending on the specific immune defect. Thus, immune status must be considered for each patient, and individual treatment planning is essential. If known, the clinical phenotypes of specific mutations can be used to guide the management of PIDs. We believe that CP may be an important choice in approaching immunodeficient COVID-19 patients, especially those with hypogammaglobulinemia, due to its high specific antibody content.

Abbreviations COVID-19: coronavirus disease 2019; CP: convalescent plasma; CVID: common variable immunodeficiency; HSCT: hematopoietic stem cell transplantation; HCQ: hydroxychloroquine; IVIG: intravenous immunoglobulin; NEMO: NF-κB essential modulator; NF-κB: nuclear factor kappa B; PCR: polymerase chain reaction; PIDs: primary immunodeficiency disease; XHIGM: X-linked hyper-IgM syndrome

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Author contribution GA, HA, SKTE, and ME were responsible for constructing an idea or hypothesis for the manuscript, patient follow-up, data management, and reporting (data collection), literature review, and the construction of the manuscript.

Declarations

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

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