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New-Onset Ocular Myasthenia after Multisystem Inflammatory Syndrome in Children

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Neurologic complications have been associated with multisystem inflammatory syndrome in children, possibly involving autoimmune mechanisms. Here, we report a 6-year-old girl who developed myasthenia 11 weeks after severe acute respiratory syndrome coronavirus 2 infection and 8 weeks after the onset of severe multisystem inflammatory syndrome in children. (J Pediatr 2022;245:213-6).

Neurologic complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children including headache, altered mental status, encephalopathy, seizures, coma, encephalitis, demyelinating disorders, and aseptic meningitis have been described. Various mechanisms of involvement are hypothesized, including direct viral injury to neural cells, vascular endothelial, and inflammatory injury. Autoimmunity and development of autoantibodies also is postulated.

Myasthenia gravis is an autoimmune disease involving dysfunction of the neuromuscular junction, with clinical phenotypes ranging from isolated ocular to generalized weakness with bulbar and respiratory involvement. Juvenile myasthenia gravis accounts for 10%-15% of all autoimmune myasthenias. Ocular myasthenia gravis is defined when symptoms are limited to the levator palpebrae superioris, orbicularis oculi, and extraocular muscles, accounting for 10%-35% of juvenile myasthenia gravis. Myasthenia gravis is triggered by both genetic and environmental causes, including infections, autoimmune diseases, and rheumatic diseases. A single pediatric patient with transient myasthenia gravis has been reported after multisystem inflammatory syndrome in children (MIS-C).

MIS-C is defined as a novel entity within 2-6 weeks of initial SARS-CoV-2 exposure and is characterized by an uncontrolled inflammatory response with multiorgan failure. The use of proteomics, RNA sequencing, autoantibody arrays, and B- and T-lymphocyte repertoire analysis have characterized factors contributing to hyperinflammation and vascular injury. Evidence has shown a strong autoimmune signature with autoantibodies targeted to both ubiquitously expressed and tissue-specific antigens and enhanced neutrophil responses tied to T-cell receptor repertoire with speculation of pathogenesis as a superantigen-driven pathogenic process. We present a child with severe MIS-C and weakness who developed ocular myasthenia gravis 11 weeks after onset of SARS-CoV-2 infection. Parental informed consent was taken to publish the case and facial photographs.

Case Report

A 6-year-old girl with previously diagnosed asthma presented with fever for 4 days, rash for 2 days, and abdominal pain 3 weeks after a positive nasopharyngeal reverse-transcription polymerase chain reaction test for SARS-CoV-2 performed because of a 2-day history of cough. She had been followed without any medication at that time. Her family history was unremarkable except for paternal coronary artery disease. She was admitted in poor general condition with tachycardia (160 beats/minute) and fever (39.1°C). She had bilateral nonsuppurative conjunctivitis, periorbital edema, and erythema and erythematous maculo-papular rash on her neck, trunk, and extremities (Figure, A-C). Extensive laboratory evaluation revealed white blood cells 6.7 × 10^9/μL (normal: 5-13 × 10^9/μL), lymphocytes 0.67 × 10^9/μL (normal: 1-5 × 10^9/μL), platelets 136 × 10^9/μL (normal: 180-400 × 10^9/μL), and elevated inflammatory markers, including C-reactive protein 18.57 mg/dL (normal: 0-0.5 mg/dL), erythrocyte sedimentation rate 30 mm/h (normal: 0-20 mm/h), procalcitonin 14.76 ng/mL (normal: 0-0.1 ng/mL), D-dimer 17.63 mg/L (normal: 0.55 mg/L), brain natriuretic peptide 98 pg/mL (normal: 0-100 pg/mL), troponin-I 23.0 ng/L (normal: 0.1-0.5 ng/L), ferritin 344 μg/L (normal: 11-307 μg/L), fibrinogen 619.1 mg/dL (normal: 180-350 mg/dL), and interleukin-6 3314 pg/mL.
Electrocardiogram revealed sinus tachycardia. Nasopharyngeal swab SARS-CoV-2 reverse-transcription polymerase chain reaction test was negative, and SARS-CoV-2 immunoglobulin G antibody was positive (1.2 [≤0.8]) by anti-SARS-CoV-2 enzyme-linked immunosorbent assay test (EUROIMMUN).

Based on the previous history of coronavirus disease 2019 (COVID-19) infection, examination, and laboratory findings, the diagnosis of MIS-C was confirmed. Echocardiography revealed tricuspid and mitral insufficiency and pericardial effusion. Oral intake was stopped due to abdominal pain and rebound tenderness. Intravenous fluids, empiric broad-spectrum antibiotic, anticoagulant, and anti-inflammatory therapy were administered: ceftriaxone, amikacin and ornidazole, favipiravir, anakinra, intravenous immunoglobulin (2 g/kg), methylprednisolone (2 mg/kg/d), and enoxaparin sodium (0.5 mg/kg/dose).

On hospital day 2, she developed persistent hypotension and respiratory distress and thus was intubated and plasma exchange was performed. Favipiravir was stopped, and remdesivir and pulse methylprednisolone (30 mg/kg) were started, to be tapered on the following days according to the clinical and laboratory status of the patient. Serum creatine kinase (CK) level was slightly increased (838 U/L; normal: ≤145) on hospital day 3 and was normal on day 5. Follow-up echocardiogram revealed dilatation of the left main coronary artery, and a single dose of intravenous immunoglobulin (0.4 g/kg) was repeated. Inotropes were stopped on hospital day 6, and she was extubated on hospital day 7. Following extubation, there was generalized flaccid muscle weakness; upper and lower extremity muscle strength was 1/5, deep tendon reflexes were decreased, leading to the possible diagnosis of intensive care unit (ICU) acquired weakness which was confirmed with electromyography demonstrating myopathic changes and normal nerve conduction velocities. Serum CK level was normal (33 U/L). Intensive physical therapy was initiated. She was discharged on hospital day 16 with muscle strength of 3-4/5. Two weeks after discharge, she was back to normal, able to run and climb stairs without support.

Six weeks after discharge, her parents documented intermittent drooping of eyelids with fatigue that was worse in...
the evenings. Bilateral ptosis was triggered by the fatigue test and improved by administration of pyridostigmine (Figure, D-F). Systemic and neurologic examinations were otherwise normal. Serum anti-acetylcholine receptor antibody (anti-AChR Ab) was positive (6.42 nmol/L; normal: <0.25). The patient was diagnosed with seropositive ocular myasthenia gravis, and response to standard dose of pyridostigmine (1 mg/kg/d) was favorable. At 4-month follow-up, she was symptom-free, and serum anti-AChR Ab continued to be positive (4.96 nmol/L). The Table summarizes the characteristics of 2 pediatric patients with new-onset myasthenia gravis following MIS-C.

Discussion

Accumulating data support immune-mediated injury to multiple organ systems following SARS-CoV-2 infection. In children, the involvement of central and peripheral nervous system of MIS-C includes a wide range of manifestations including muscle weakness, paresthesia, headache, meningismus/meningitis, and encephalopathy. However, long-term follow-up is required to assess for neurologic complications of pediatric patients with varying severity of MIS-C. Extensive immune-profiling studies showed that immune response in MIS-C is distinct from that during acute SARS-CoV-2 infection; MIS-C is characterized by activated innate immune cells and appropriate antibody responses detected against SARS-CoV-2. MIS-C as a hyperinflammatory syndrome has been explained through the “superantigen hypothesis,” with superantigen-like sequence motif expressed on SARS-CoV-2 spike protein exhibiting a high affinity to bind to T-cell receptors. Next-generation immunosequencing analysis has revealed both T- and B-lymphocyte repertoire abnormalities in patients with mild and severe MIS-C.

Although the course of SARS-CoV-2 infection in patients with myasthenia gravis, with aggravation of myasthenic symptoms, are well-described, development of new-onset myasthenia gravis has been rarely documented in children and adults. Initially, autoimmune myasthenia gravis was diagnosed in 3 adults with generalized fatigue during COVID-19, positive anti-AChR Ab, and decremental electromyography responses to repetitive nerve stimulation. This association was further detailed in an adult series including 9 patients showing a temporal relationship with SARS-CoV-2 infection. The majority of the affected patients were older than 50 years; male to female 5:4; time interval between infection and myasthenia gravis 5-56 days; generalized, bulbar and/or ocular symptoms; presence of anti-AChR Ab and antimuscle-specific kinase antibodies; and improvement with immunotherapy.

The only pediatric patient reported to date was a 7-year-old girl who developed new-onset transient ocular myasthenia gravis with an AChR Ab–positive titer of 0.51 nm/L (normal: <0.39) shortly after recovery from severe MIS-C, ICU-acquired weakness, post–COVID-19 myositis, with a time lag between initial symptoms of 18 days. Although she responded initially to pyridostigmine, corticosteroid and methotrexate were given due to suboptimal response, and there was complete resolution of the symptoms 1 month after discharge. Anti-AChR Ab and SARS-CoV-2 antibody tests were negative, leading to slow discontinuation of pyridostigmine and corticosteroids.

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Time lag between severe MIS-C and new-onset ocular myasthenia gravis was 8 weeks in our patient, who had a favorable response to pyridostigmine treatment, requiring no additional pharmacotherapy. She was symptom-free at a 4-month follow-up visit, although serum anti-ACHR Ab was still positive. Prepubertal myasthenia gravis is more prevalent in male patients and usually is seronegative. We

Table. Characteristics of pediatric patients with new-onset myasthenia gravis following COVID-19

| Characteristics                              | Case 1 | Case 2 (current patient) |
|----------------------------------------------|--------|--------------------------|
| Age, y                                       | 7      | 6                        |
| Sex                                          | Female | Female                   |
| Country of origin                            | South Africa | Turkey                  |
| SARS-CoV-2 nasopharyngeal swab               | N/A    | (+)                      |
| RT-PCR test                                  |        |                          |
| Time lag between SARS-CoV-2 and MIS-C, wk    | 2      | 3                        |
| Presenting MIS-C symptoms                    |        |                          |
| SARS-CoV-2 RT PCR/Ab at MIS-C presentation   | (–)/(+)| (–)/(+),                  |
| Time lag between onset of MIS-C symptoms and hospitalization, d | 5      | 5                        |
| Length of ICU stay, d                        | 15     | 16                       |
| Serum CK level, U/L                          | 6617   | 838-33 (normal: ≤145)    |
| Ptosis onset after MIS-C diagnosis           | 18 d   | 8 wk                     |
| Anti-AChR Ab, nmol/L                         | 0.51 (≤0.39) | 6.42 (normal: <0.25)    |
| Treatment                                    | Pyridostigmine, low-dose oral corticosteroids, methotrexate | Pyridostigmine |
| Follow-up duration, mo                       | 1 mo   | 4                        |
| Final examination/anti-AChR Ab status        | Normal/(–) | Normal/(+)              |
| Final diagnosis                              | New-onset transient ocular myasthenia gravis | New-onset ocular myasthenia gravis |

N/A, not available; RT-PCR, reverse-transcription polymerase chain reaction.
speculate that an exaggerated interferon pathway response may be a risk factor for the development of autoantibodies such as those directed against AChR in our case.

New-onset myasthenia gravis following hepatitis B and C, herpes simplex, HIV, varicella-zoster, West Nile, and Zika virus infections has been reported.17-19 As in our patient, myasthenia gravis occurring following SARS-CoV-2 infection is also possible. Although there is no documented direct link between any specific preceding infection and myasthenia gravis, suggested mechanisms for this temporal association can be epitope homology/molecular mimicry between surface proteins of the virus and the acetylcholine receptor, epitope spreading, bystander activation, immortalization of infected B lymphocytes, loss of immunologic self-tolerance, and drug-induced exacerbation.15,19,20

There was a mild increase in serum CK level in our patient on hospital day 3 of MIS-C admission, correlating with the greatest serum interleukin-6 level. Within 3 days, her serum CK level returned to normal. This slight increase may be due to various mechanisms such as muscle inflammation during the disease course.21 Prolonged ICU stay, use of corticosteroids, electrophysiologic findings, course of the weakness and total recovery were compatible with ICU-acquired weakness, which should be separately evaluated in children with MIS-C. Our case highlights the association of SARS-CoV-2 infection with MIS-C and myasthenia gravis as an autoimmune complication and cautions the need for prolonged observation.

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