Neurological Manifestations of Multisystem Inflammatory Syndrome in Children

Çocuklarda Multisistem İnflamatuvar Sendromun Nörolojik Bulguları

Deniz YILMAZ, Esra GURKAS, Aysegul Nese CITAK KURT

Ankara City Hospital, Department of Pediatric Neurology, Ankara, Turkey

ABSTRACT

Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 first reported from South East London has a wide spectrum of neurological signs and symptoms including headache, impaired consciousness, aseptic meningitis, encephalitis, seizure, ataxia, and stroke. It is important to diagnose these patients as soon as possible and treat them with a multidisciplinary approach. A few studies have reported post-discharge follow-up data in MIS-C patients with neurological symptoms most of whom showed neurological improvement. Long-term follow-up of MIS-C patients is required to determine possible neurological sequelae.

Key Words: COVID-19, MIS-C, Neurological manifestations

ÖZ


Anahtar Kelimeler: COVID-19, MIS-C, Nörolojik bulgular

INTRODUCTION

The novel coronavirus, Corona Virus Disease 2019 (COVID-19), which was identified after a recent outbreak in Wuhan, China, in December 2019, is currently a global pandemic (1). Typical clinical presentations include fever, cough, dyspnea, anosmia, and myalgia (1,2). Angiotensin-converting enzyme 2 (ACE2) receptor, which is the entry point for COVID-19 is present in human organs including lung parenchyma, gastrointestinal tract, nasal mucosa, human airway epithelia, lymphoid tissues, vascular endothelium, smooth muscle cells, glial cells and neurons which also makes the brain a possible target of COVID-19. Another cell membrane protein transmembrane serine protease 2 (TMPRSS2) expressed in some glial cells of animal models is also a target necessary for SARS-CoV-2 invasion. However, the degree of expression is unclear for both proteins (1-4).

Neurological manifestations of COVID-19 such as change in mental status, encephalitis, hypoguesia are being reported with each passing day (5,6). The rate of neurological findings varies between 7.7-57.4% in different studies (7,8). However, neurological involvement in children with COVID-19 appears to be limited or under reported (9). Children seemed to be only mildly symptomatic with the infection in most cases until Riphagen et al. (10) had reported 8 previously healthy children from South East London with hyperinflammatory shock, a syndrome exhibiting features similar to atypical Kawasaki disease. These children had no significant respiratory issues and were mostly negative for SARS-CoV-2 but exposed to SARS-CoV-2 subjects. Thereafter similar presentations were reported from other areas as well (10-13). The Royal College of Paediatrics and Child Health (RCPCH) referred to this acute condition as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) (14). Later on...
the illness was labelled multisystem inflammatory syndrome in children (MIS-C) by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) based on 6 principle elements: pediatric age, persistence of fever, presence of laboratory markers of inflammation, manifestation of signs or symptoms of organ dysfunction, lacking an alternative diagnosis, and a temporal relation to COVID-19 infection or exposure (12,14-16). The defining features are presented in table I.

MIS-C is thought to occur in genetically susceptible individuals with hyperinflammatory response after SARS-CoV-2 infection (17). Children with delayed type I and type III interferon responses after COVID-19 infection may have a higher risk of developing cytokine storm and MIS-C (18). In a large series of MIS-C patients from the United States, a total of 570 children who met the case definition of CDC were reported. The illness in 490 (86.0%) patients involved ≥ 4 organ systems and most of the neurological symptoms developed in these patients. Headache was the most common neurological symptom (19).

Neurological manifestations reported in patients with MIS-C are headache, impaired consciousness, aseptic meningitis, encephalitis, seizure, ataxia and stroke (9,20). According to a systematic review of eight studies, the incidence of neurological symptoms in children with MIS-C was 25-50% (9). Kaushik et al. (21) reported neurological symptoms in 12-58% of affected children. Similar neurological findings were reported in studies by Whittaker et al. (22), and Chiotos et al. (23). Among children diagnosed with MIS-C in New York neurological symptoms including headache, altered mental status, and encephalopathy were seen in 31-47% (4). Another study in the United States found that only 5% of MIS-C patients suffered from severe neurological complications such as seizure, coma, encephalitis, demyelinating disorders, and aseptic meningitis (24). The reported patients with laboratory findings, neuroimaging and/or neurophysiologic evaluation, immunotherapy and outcome in addition to neurological symptoms are shown in table II.

Treatment regimen includes antiviral therapy (if PCR positive for SARS-CoV-2), immunotherapy, inotropic support, anticoagulation and plasma therapy. Vital signs, hydration, electrolytes and metabolic status should be monitored. Steroids, intravenous immunoglobulin (IVIG), infliximab (anti-tumour necrosis factor drug), tocilizumab (IL-6 antagonist) and anakinra (IL-1 receptor antagonist) are the treatment choices (4,32).

MIS-C has a wide spectrum of neurological signs and symptoms ranging from myalgia to encephalopathy. Patients with MIS-C
### Table II: Neurological symptoms, laboratory and imaging findings, immunotherapy and outcome of the patients.

<table>
<thead>
<tr>
<th>First Author/number of patients</th>
<th>Neurological symptoms</th>
<th>Laboratory parameters</th>
<th>Neuroimaging</th>
<th>Neurophysiologic evaluation</th>
<th>Immunotherapy/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abel25/1</td>
<td>Somnolence, hypotonia, weakness</td>
<td>High CRP, ferritin, IL-6, NT-proBNP; low platelet count</td>
<td>Restricted diffusion in the bilateral lateral thalamic nuclei</td>
<td>-</td>
<td>Intravenous methylprednisolone, intravenous immunoglobulin, anakinra / Mild residual weakness</td>
</tr>
<tr>
<td>Abdel-Mannan26/4</td>
<td>Headache, encephalopathy, ataxia, meningism, dysarthria, dysphagia, muscle weakness, hyporeflexia</td>
<td>High CRP, D-dimer, LDH, ferritin</td>
<td>Restricted diffusion (n=3) and signal changes of the genu and the splenium of the corpus collosum (n=4)</td>
<td>Mild myopathic or neuropathic changes (n=3)</td>
<td>Intravenous methylprednisolone (n=2), dexamethasone (n=2), intravenous immunoglobulin (n=2), anakinra (n=2), and rituximab (n=1) / Fully recovered (n=2), wheelchair bound(n=2)</td>
</tr>
<tr>
<td>Chiotos/3</td>
<td>Headache/dizziness (n = 1), lethargy/ altered mental state (n = 2)</td>
<td>Low lymphocyte%, albumin; high CRP, D-dimer, PCT, LDH, BNP, troponin</td>
<td>Diffuse cerebral edema (n=1)</td>
<td>-</td>
<td>Intravenous methylprednisolone (n=3), intravenous immunoglobulin (n=3) / Discharged home</td>
</tr>
<tr>
<td>Dugue 27/1</td>
<td>Brief episodes of sustained upward gaze, bilateral leg stiffening</td>
<td>High PCT; low leukocyte</td>
<td>Normal</td>
<td>-</td>
<td>- / Fully recovered</td>
</tr>
<tr>
<td>Oualha28/1</td>
<td>Right-sided weakness, altered consciousness</td>
<td>High CRP</td>
<td>Sphenoidal sinusitis with cavernous sinus thrombosis</td>
<td>-</td>
<td>Not mentioned/Died</td>
</tr>
<tr>
<td>Regev29/1</td>
<td>Headache, nuchal rigidity, muscle weakness, and clonus</td>
<td>High CRP, D-dimer, NT-proBNP, troponin; mild elevation INR; low C3, C4 factors; normal fibrinogen</td>
<td>Diffuse brain hemosiderosis</td>
<td>-</td>
<td>Intravenous methylprednisolone, intravenous immunoglobulin / Normal apart from general muscle weakness.</td>
</tr>
<tr>
<td>Shenker29/1</td>
<td>Trismus, loss of smell and taste, difficulty swallowing, altered mental status, status epilepticus</td>
<td>High CRP, CK, BNP, D-dimer, ESR, ferritin, fibrinogen, IL-6, LDH, PCT</td>
<td>Normal</td>
<td>-</td>
<td>Intravenous immunoglobulin, remdesivir, anakinra / Mental status resolved, seizures continued despite antiepileptic drugs</td>
</tr>
<tr>
<td>Verkuil31/1</td>
<td>Headache, myalgia, eye movement restriction</td>
<td>High CRP, fibrinogen; normal INR</td>
<td>Eversion of the right optic disc, flattening of the posterior right globe; widened right and left optic nerve sheath diameters, flattened upper border of the pituitary gland, narrowing of the transverse sinuses</td>
<td>-</td>
<td>Intravenous methylprednisolone, intravenous immunoglobulin / Fully recovered</td>
</tr>
</tbody>
</table>

**BNP**: Brain natriuretic peptide, **CK**: Creatine kinase, **CRP**: C-reactive protein, **ESR**: Erythrocyte sedimentation rate, **IL**: Interleukin, **INR**: International normalized ratio, **LDH**: Lactate dehydrogenase, **NT-proBNP**: N-terminal pro B-type natriuretic peptide, **PCT**: Procalcitonin, **PT**: Prothrombin time, **PTT**: Partial thromboplastin time, **RT-PCR**: reverse transcription-polymerase chain reaction
should be treated with a multi-disciplinary approach. A few studies have reported post-discharge follow-up data in MIS-C patients with neurological symptoms most of whom showed neurological improvement. Long-term follow-up of MIS-C patients is required to determine possible neurological sequelae.

REFERENCES