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Neurological Manifestations of Multisystem Inflammatory Syndrome in Children

Çocuklarda Multisistem İnflamatuvar Sendromun Nörolojik Bulguları

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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 ap-proach. 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

İlk olarak Londra'nın güneydoğusunda bildirilen çocuklarda COVİD-19 ile ilişkili multisistem inflamatuvar sendromun (MIS-C) nörolojik bulguları baş ağrısı, bilinç değişikliği, aseptik menenjit, ensefalit, nöbet, ataksi ve inme gibi geniş bir nörolojik belirti ve semptom yelpazesine sahiptir. Bu hastalara mümkün olan en kısa sürede tanı koymak ve multidisipliner bir yaklaşımla tedavi etmek önemlidir. Nörolojik semptomları olan ve çoğu nörolojik açıdan düzelme gösteren MIS-C hastalarında taburculuk sonrası takip ile ilgili az sayıda çalışma vardır. MIS-C'ye bağlı gelişmesi olası nörolojik sekelleri belirlemek için uzun vadeli takip gerekmektedir.

Anahtar Kelimeler: COVİD-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

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Table I: Case definitions for MIS-C from Centers for Disease Control and Prevention and the World Health Organization.

Centers for Disease Control and Prevention	World Health Organization
An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac,kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever>38.0°C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin **AND** No alternative plausible diagnoses **AND** Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms ***Additional comments*** Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection	Children and adolescents 0–19 years of age with fever ≥3 days. **AND** ***two of the following:*** 1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiography findings or elevated Troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers) 5. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain) **AND** Elevated markers of inflammation such as ESR, CRP or procalcitonin **AND** No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes **AND** Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

CRP: *C-reactive protein,* ***ESR:*** *erythrocyte sedimentation rate,* ***IL:*** *interleukin,* ***LDH:*** *lactate dehydrogenase,* ***NT-proBNP:*** *N-terminal pro-B-type natriuretic peptide,* ***PT:*** *prothrombin time,* ***PTT:*** *partial thromboplastin time,* ***RT-PCR:*** *reverse transcription-polymerase chain reaction.*

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.

First Author/ number of patients	Neurological symptoms	Laboratory parameters	Neuroimaging	Neurophysiologic evaluation	Immunotherapy/Outcome
Abel[25]/1	Somnolence, hypotonia, weakness	High CRP, ferritin, IL-6, NT-proBNP; low platelet count	Restricted diffusion in the bilateral lateral thalamic nuclei	-	Intravenous methylprednisolone, intravenous immunoglobulin, anakinra / Mild residual weakness
Abdel-Mannan[26]/4	Headache, encephalopathy, ataxia, meningism, dysarthria, dysphagia, muscle weakness, hyporeflexia	High CRP, D-dimer, LDH, ferritin	Restricted diffusion (n=3) and signal changes of the genu and the splenium of the corpus collosum (n=4)	Mild myopathic or neuropathic changes (n=3)	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)
Chiotos/3	Headache/dizziness (n = 1), lethargy/ altered mental state (n = 2)	Low lymphocyte%, albumin; high CRP, D-dimer, PCT, LDH, BNP, troponin	Diffuse cerebral edema (n=1)	-	Intravenous methylprednisolone (n=3), intravenous immunoglobulin (n=3) / Discharged home
Dugue [27]/1	Brief episodes of sustained upward gaze, bilateral leg stiffening	High PCT; low leukocyte	Normal	-	-/Fully recovered
Oualha[28]/1	Right-sided weakness, altered conciousness	High CRP	Sphenoidal sinusitis with cavernous sinus thrombosis	-	Not mentioned/Died
Regev[29] /1	Headache, nuchal rigidity, muscle weakness, and clonus	High CRP, D-dimer, NT-proBNP, troponin; mild elevation INR; low C3, C4 factors; normal fibrinogen	Diffuse brain hemosiderosis	-	Intravenous methylprednisolone, intravenous immunoglobulin /Normal apart from general muscle weakness.
Shenker[30]/1	Trismus, loss of smell and taste, difficulty swallowing, altered mental status, status epilepticus	High CRP, CK, BNP, D-dimer, ESR, ferritin, fibrinogen, IL-6, LDH, PCT	Normal	-	Intravenous immunoglobulin, remdesivir, anakinra / Mental status resolved, seizures continued despite antiepileptic drugs
Verkuil[31]/1	Headache, myalgia, eye movement restriction	High CRP, fibrinogen; normal INR	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	-	Intravenous methylprednisolone, intravenous immunoglobulin / Fully recovered

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.

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