



BRAIN IMAGING (CT & MRI) IN CHILDREN WITH MULTI INFLAMMATORY SYSTEMIC SYNDROME (MIS-C)

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Abstract

Background: Multi Inflammatory Systemic Syndrome (MIS-C) has been identified in multiple countries impacted by the COVID-19 pandemic. MRI is valuable for assessing neurologic deficits after MIS-C and can help guide treatment decisions. The aim of this study is to assess the clinical and radiological findings of brain involvement in children with SARS-CoV-2 infection and MIS-C.

Methods: This cross-sectional observational study was conducted at PICU of our institution, including 25 children diagnosed as MIS-C clinically and laboratory (according to CDC & WHO guidelines) with neurological signs and symptoms (including irritability, GCS disturbances and others).

Collected data included brain imaging by CT and MRI studies showing abnormal signals within both cerebral hemispheres, brain stem and cerebellum.

Results: This study included 25 patients. All diagnosed as MIS-C with neurological signs and symptoms. All patients underwent brain imaging including CT and/or MRI studies. About 60% of cases have positive findings. CT examinations were normal in 15 patients and revealed brain alterations in seven (31.8%). MRI findings were the nonspecific hyperintense signal in T2WI and FLAIR and restricted diffusion in DWI (80% and 73.3% respectively), followed by the ischemic infarctions that represent 47.7% of examined cases. Hemorrhage that was represented in one case.

Conclusions: Some children with MIS-C showed brain involvement and were presented with neurological symptoms involving both the central and peripheral nervous systems. On imaging, they were represented with different cerebral, cerebellar and brain stem lesions that mainly show nonspecific hyperintense signal in T2WI & FLAIR and restricted diffusion in DWI by MRI examination as well as hypodense areas by CT examination.

Keywords: Multi Inflammatory Systemic Syndrome, Brain Imaging, children.

Background:

Over 250 million people infected, 5 million deaths from SARS-CoV-2 since December 2019 (1). Unlike adults, most children with COVID-19 exhibit mild symptoms. However, there are children who have considerable respiratory disease, and some children may develop a hyper-inflammatory response similar to that observed in adults with COVID-19 (2).

Most common presentation: flu-like illness progressing to severe pneumonia, respiratory distress, shock, and death (3)

MIS-C has been detected in several countries impacted by the COVID-19 pandemic. Since spring 2020, Western nations call it Kawasaki-like disease. MIS-C causes hyperinflammation, leading to macrophage activation syndrome or cytokine storm, as reported by Kabeerdoss et al. (4).

Multiple systems involved; nervous system significant. Studies show neurological symptoms related to SARS-CoV-2 in adults. Reported symptoms: headache, hyposmia, stroke and Guillain–Barre syndrome (1). Patients recovering from infection can have long-lasting cognitive impairments in "long COVID" (5).

MIS-C patients often need hospitalization and pediatric intensive care unit (PICU) admission (6). Many also show neurological symptoms (7).

Imaging findings of MIS-C associated with COVID-19 vary based on which part of the body is affected by inflammation. Although some studies have found that radiological findings are not specific enough to be used as a diagnostic tool, they can still help doctors identify potential cases of MIS-C. So, while imaging alone may not be enough to make a diagnosis, it's still an important tool for doctors to have in their talk it (8).

Brain MRI is valuable for assessing neurologic deficits post MIS-C and guiding treatment decisions (9).

Brain MRI can reveal abnormal signals, inflammation, and lesions in different parts of the brain. They can also determine whether these areas are affected by blood clots or bleeding. All of this information helps doctors figure out the best way to treat the child and prevent any further complications (8).

Objectives:

The aim of this study is to assess the clinical and radiological findings of brain involvement in children with SARS-CoV-2 infection and MIS-C.

Methods:

This a cross section randomized clinical study was performed on twenty-five patients, with an age range from 3 months to 13 years (mean age 3.2 ± 10.716 years), with neurological symptoms out of 176 patients fulfill criteria of MIS-C out of 312 patients suspected or confirmed COVID-19 within the 4 weeks prior to the onset of symptoms. The study was done at the Pediatric, neonatal intensive care unit, intermediate care unit and emergency department in our institution from January to June 2022.

Inclusion criteria: This study included children, aged 0-18 years, included both sexes, came with neurological symptoms and fulfill criteria of MIS-C (WHO) (10). According to CDC criteria exposure to a patient with suspected or confirmed COVID-19 within the 4 weeks prior to the onset of symptoms (11).

Exclusion criteria: Patients older than 21 years

, patients with no neurological symptoms, patients with multi-inflammatory system disease and not proved to be COVID-19 like Kawasaki disease. Other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/streptococcal toxic shock syndromes.

Clinical assessment: All patients were subjected to the following: History taking include age, sex, and history of exposure to infection. Clinical examination (general and neurological). Investigation: laboratory :CBC , ESR, CRP, Liver and renal function, Cardiac enzyme, ABG, Na , K, Ferritin, D-dimer, IL 6 .b-Radiological :chest x-ray, Echo, Abdominal Ultrasound, c-brain imaging :

1-CT brain: CT scanners (Siemens Somatom 16 slice), CT machines were used in study using non contrast axial, sagittal and coronal cuts.

2-MRI brain : Philips Achieva 1.5 Tesla, MRI machine was used in the study using multiple sequences including non-contrast sagittal T2WI sequence, axial T2WI, coronal T2 WI and sagittal T1WI in most of the cases.

Statistical Analysis:

-The collected data were coded, tabulated, and statistically analyzed using the SPSS program (Statistical Package for Social Sciences) software version 26.

-Descriptive statistics were done for parametric quantitative data by mean, standard deviation, and minimum & maximum of the range, while they were done for categorical data by number and percentage.

-Analyses were done for parametric quantitative data using paired samples T-test. -The level of significance was taken at (P-value < 0.05)

Results:

The age of our study group twenty-five children ranged from 3 months - 13 years old with a mean age of 3.2 ± 10.716 years. The body weight range was 3-35 kgs. **Table (1)**

According to investigations, all patients had positive Rapid Antigenic Test For Covid (IGM recent, Igg old), 96% had negative PCR for COVID. The majority of patients had increased ESR, LDH, D-Dimer and CRP with decreased serum sodium **Table (2)**.

According to the general signs, the majority of patients came with fever (96%). About 8 out of 25 patients had circulatory shock and six patients had dyspnea. Only one child in this study came with rash.

According to GCS, 32% came with mild brain injury (GCS 13-15), 40% with moderate injury (GCS 8-12), and 7 patients (28%) came with severe brain injury (GCS <8). Mean \pm SD was 11.16 ± 8.13 . The neurological signs were divided into central and peripheral signs, The most frequent central neurological sign was seizures as 14 child had seizures while ten children complaint of paresis. Only 12% of patients had persistent headaches and abnormal movements.

The majority of children had muscle weakness and hyporeflexia (68%) and only one patient had visual changes. **Table (3)**

According to radiological manifestations **Table (4)**, brain CT was done in 22 patients (88%), the CT examinations were normal in 15 patients, and revealed brain alterations in seven (31.8%). In 6 patients, it revealed hypodensities (infarctions), and only in one case, it showed brain haemorrhage.

Figure (1)

Brain MRI was done in 15 patients (60%), the MRI examinations were normal in one case. The most common MRI findings were the nonspecific hyperintense signal in T2WI and FLAIR and restricted diffusion in DWI (80% and 73.3% respectively), followed by the ischemic infarctions that represent 47.7% of examined cases. The least common finding was the haemorrhage that was represented in one case. **Figure (2)**

According to the affected sites in brain, the most common affected sites were the corona radiata and centrum semi oval (24%), followed by lentiform nuclei (20%), then the occipital regions and corpus

callosum (16%), then the brain stem, cerebellum and thalami (12%), and the least common sites were the internal capsule and the ventricles (4%). **Figure (3)**

Table (1): Patient characteristics of the study group:

Age (in years)	Range	(0.25-13)
	Mean± SD	3.2±10.716
Weight (kg)	Range	(3-35)
	Mean± SD	12.96± 7.22
Sex	Male	12 (48%)
	Female	13 (52%)

Table (2): Investigations of the patients (n=25)

Investigation	Result	Frequency	Percent
Rapid Antigenic Test for Covid (IGM recent, Igg old)	Positive	25	100%
	Negative	0	0%
PCR for COVID	Positive	1	4%
	Negative	24	96%
Serum sodium	Decreased	16	64%
	Normal	9	36%
ESR	Increased	20	80%
	Normal	5	20%
D-Dimer	Increased	21	84%
	Normal	4	16%
CRP	Increased	22	88%
	Negative	3	12%
LDH	Increased	20	80%
	Normal	5	20%

Table (3): General and neurological signs (n=25)

Signs	Frequency	Percent	
General signs	fever	24	96%
	dyspnea	6	24%
	circulatory shock	8	32%
	rash	1	4%
Glasgow Coma Scale (GCS) "brain injury"	Mild (≥ 13)	8	32%
	Moderate (9-12)	10	40%
	Severe (≤ 8)	7	28%
	Mean± SD	11.16±8.13	
Central neurological signs	persistent headache	3	12%
	Impaired GCS	18	72%
	seizures	14	56%
	abnormal movement	3	12%
	paresis	10	40%
Peripheral neurological signs	visual changes	1	4%
	muscle weakness		68%
	hypo/areflexia	17	68%

Table (4): Radiological manifestations.

	Radiology	Frequency	Percent
CT (n=22 “88%”)	Normal	15	68.2%
	Infarction	6	27.3%
	Hemorrhage	1	4.5%
MRI (n=15 “60%”)	Normal	1	6.7%
	ischemic infarcts	7	47.7%
	intracranial hemorrhage	1	6.7%
	non specific hyperintense t2/flair	12	80%
	restricted diffusion	11	73.3%
Sites (n=25)	Thalamus	3	12%
	Corpus callosum	4	16%
	Lentiform nucleus	5	20%
	Internal capsule	1	4%
	Centrum semi oval	6	24%
	Corona radiata (parietal)	6	24%
	Occipital	4	16%
	intraventricular	1	4%
	Brain stem	3	12%
	Cerebellum	3	12%

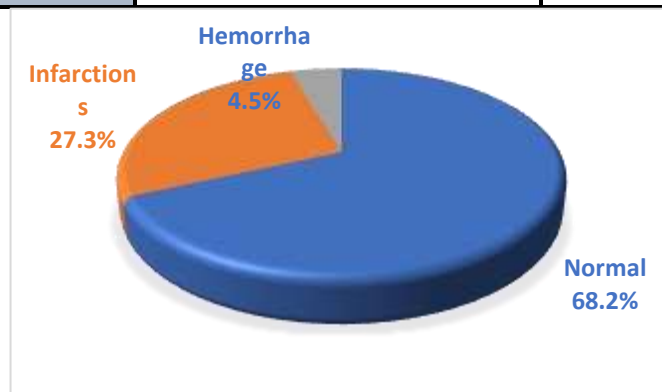


Figure (1): CT findings.

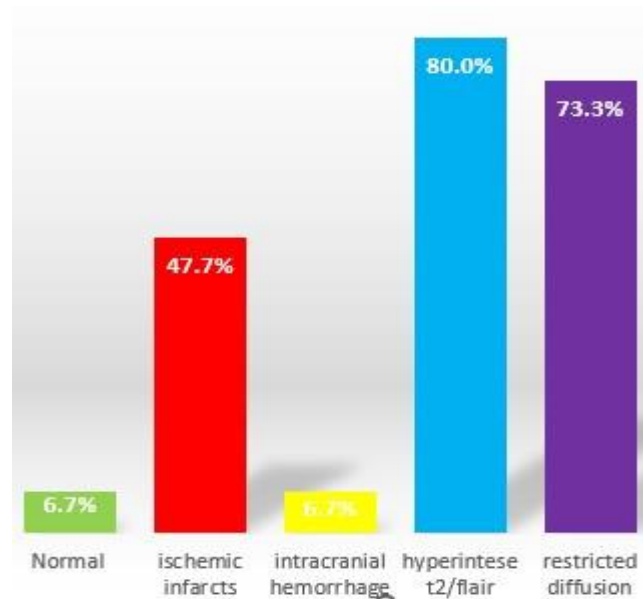
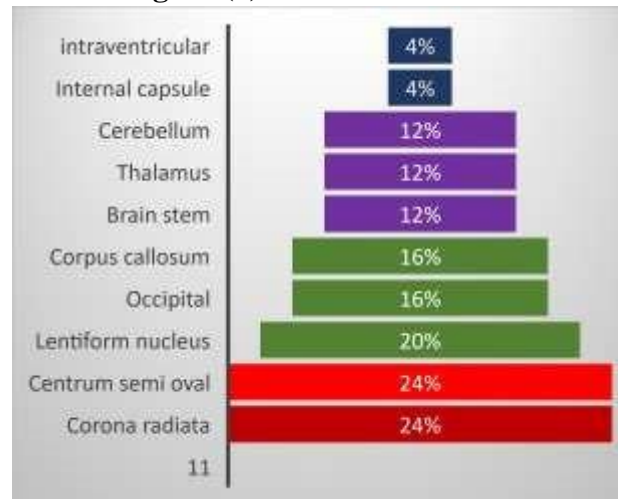


Figure (2): MRI findings.

Figure (3): the involved sites.



Cases Presentation:

Case 1. Female child 4-year-old, diagnosed as MIS-C with neurological manifestations, CT and MRI findings suggest acute ischemic infarcts. (A) and (B) axial CT images show hypodense areas at left parietal and occipital regions. (C) and (D) axial T2W MRI images, (E) and (F) axial DWIs, (G) and (H) axial and coronal FLAR; showing left lentiform nucleus, parietal and occipital hyper signal intensities, and restricted diffusion.



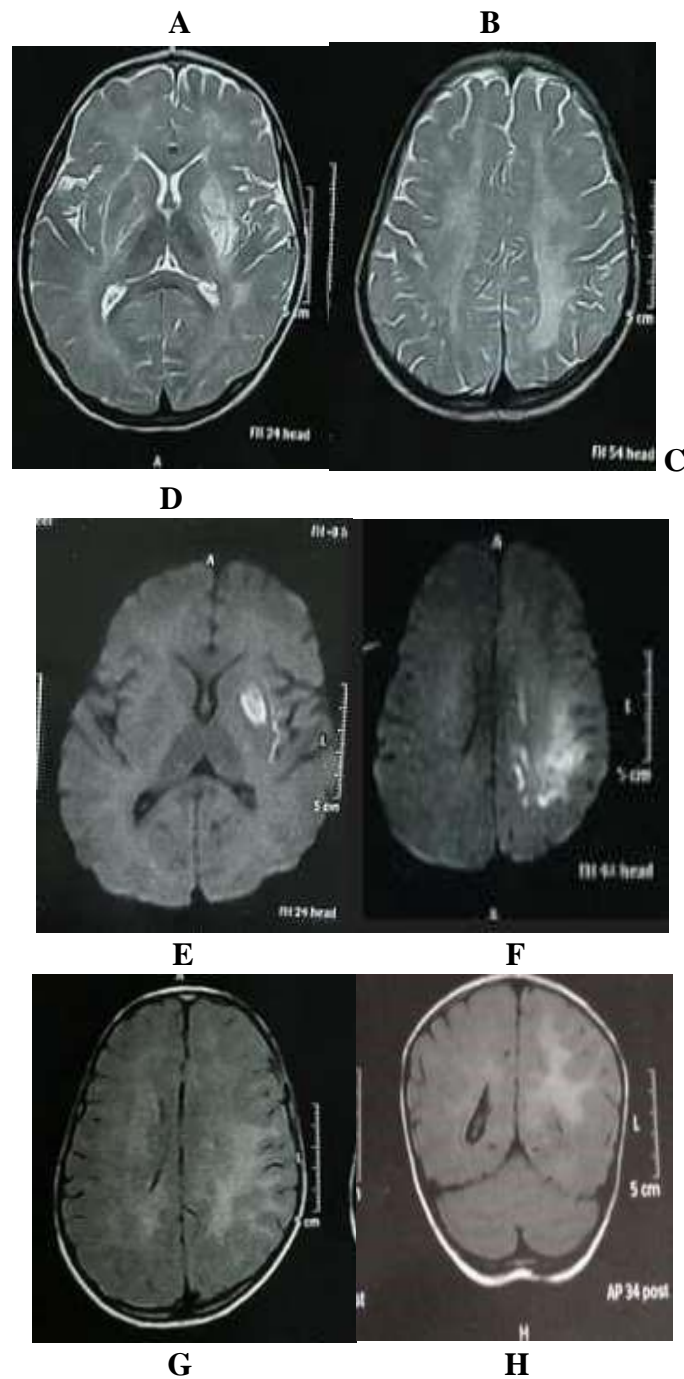
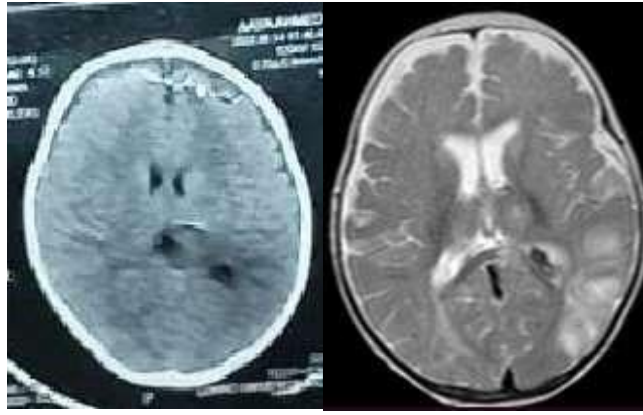
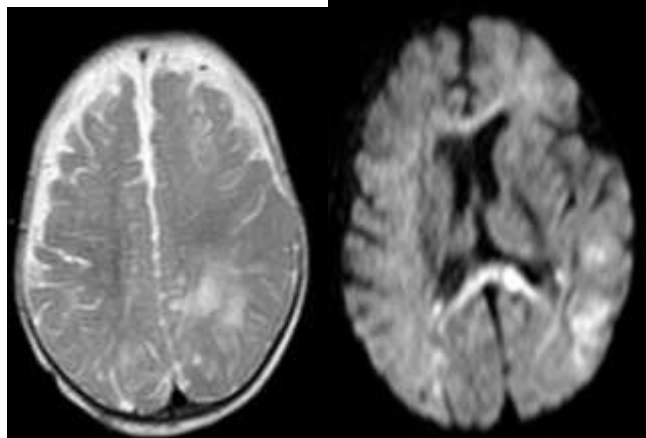


Figure 4 (A) and (B) axial CT images show hypodense areas at left parietal and occipital regions. (C) and (D) axial T2W MRI images, (E) and (F) axial DWIs, (G) and (H) axial and coronal FLAR; showing left lentiform nucleus, parietal and occipital hyper signal intensities, and restricted diffusion. **Case 2.** Female child 9-months, diagnosed as MIS-C with neurological manifestations, CT and MRI findings suggest acute ischemic infarcts. (A) axial CT images show hypodense areas at both parietal and occipital regions. (B) and (C) axial T2W MRI images, (D) and (E) axial DWIs, (F) and (G) axial FLAR; showing corpus callosum, both parietal and occipital hyper signal intensities and restricted diffusion.



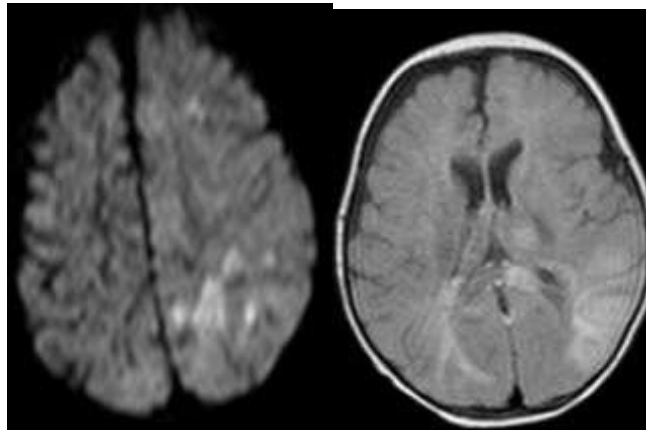
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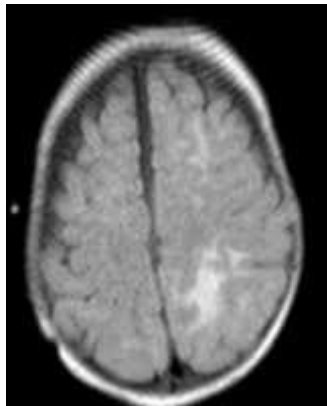
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Figure 5 (A) axial CT images show hypodense areas at both parietal and occipital regions. (B) and (C) axial T2W MRI images, (D) and (E) axial DWIs, (F) and (G) axial FLAIR; showing corpus callosum, both parietal and occipital hyper signal intensities and restricted diffusion.

Case 3. Female child 10-year-old, diagnosed as MIS-C with neurological manifestations. CT and MRI findings suggest acute hemorrhagic cerebritis with intraventricular extension. (A) axial CT images show hyperdense signal. (B) axial T1WI, show hyper intense signal within splenium of corpus callosum and left lateral ventricle, (C) axial T2 MRI images, show mixed hyper and hyposignal, (D) axial T2FFE show blooming signal, (E) axial FLAIR show mixed hyper and hyposignal intensity, (F) axial DWIs show partial restricted diffusion.

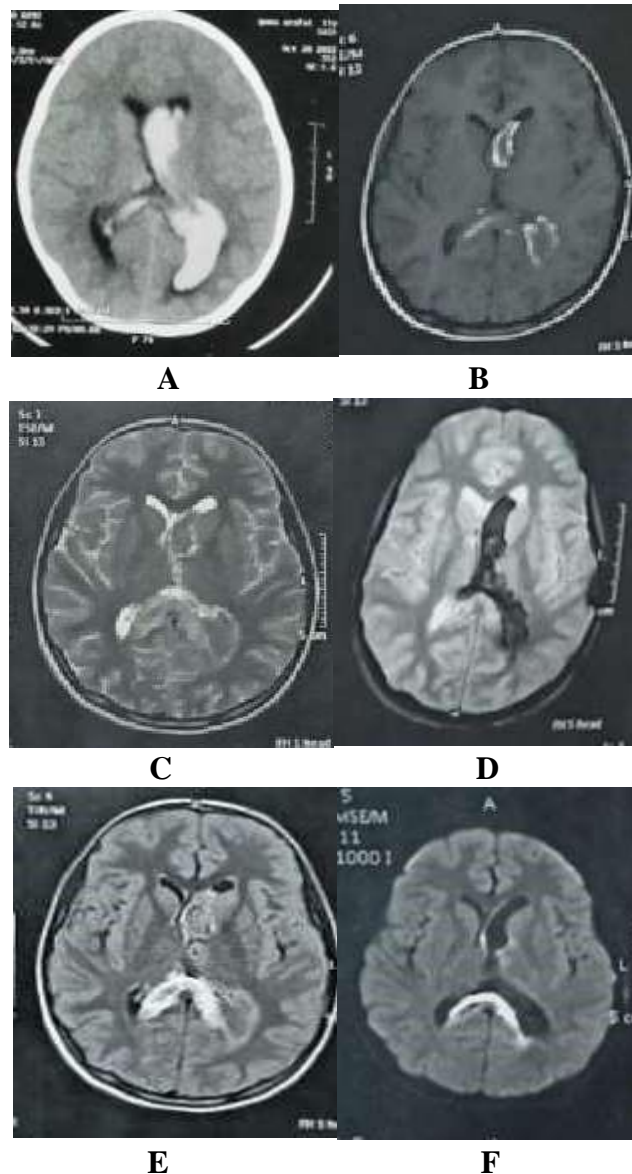


Figure 6 (A) axial CT images show hyperdense signal. (B) axial T1WI, show hyper intense signal within splenium of corpus callosum and left lateral ventricle, (C) axial T2 MRI images, show mixed hyper and hyposignal, (D) axial T2FFE show blooming signal, (E) axial FLAIR show mixed hyper and hyposignal intensity, , (F) axial DWIs show partial restricted diffusion

Case 4. Male child 3.5-year-old, diagnosed as MIS-C with neurological manifestations. CT and MRI findings suggest acute cerebritis affecting brain stem, cerebellar vermis, both thalami, both lentiform

nuclei. (A) and (B) axial T2W MRI images, (C) and (D) axial DWIs, (E) and (F) axial a FLAR showing brain stem, cerebellar vermis, both thalamic, both lentiform nuclei hyper signal intensities and restricted diffusion

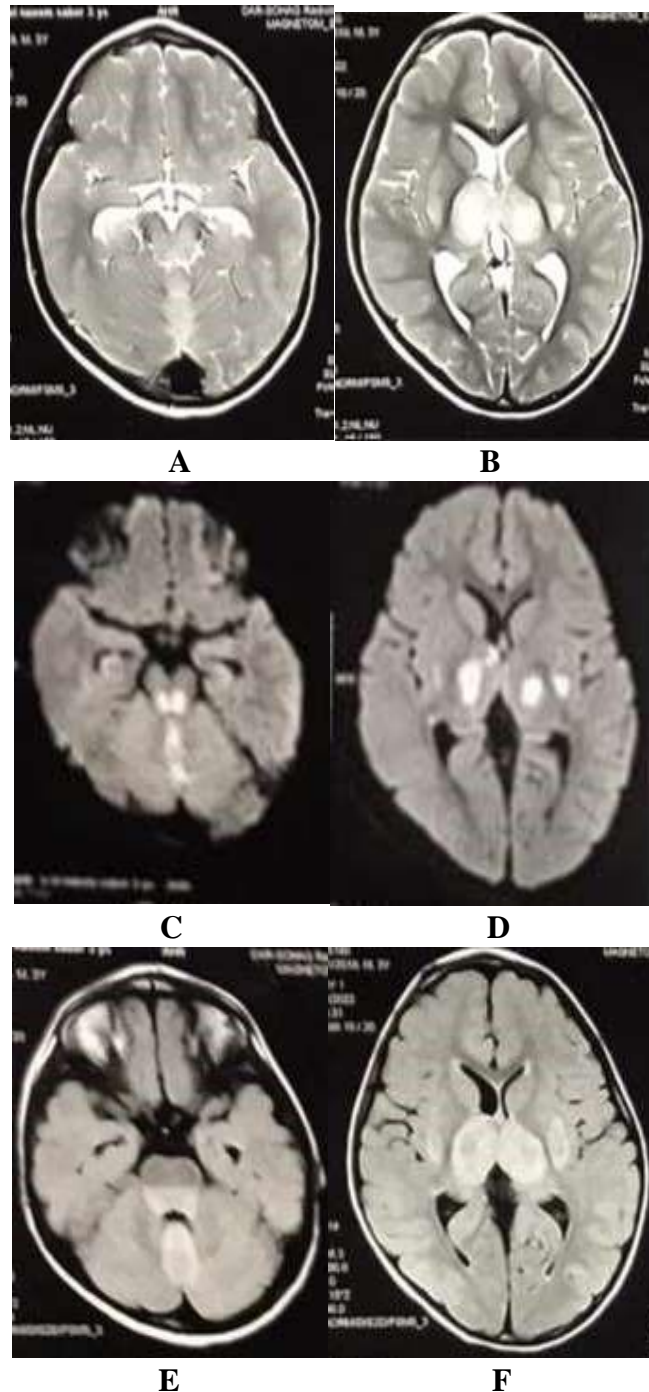
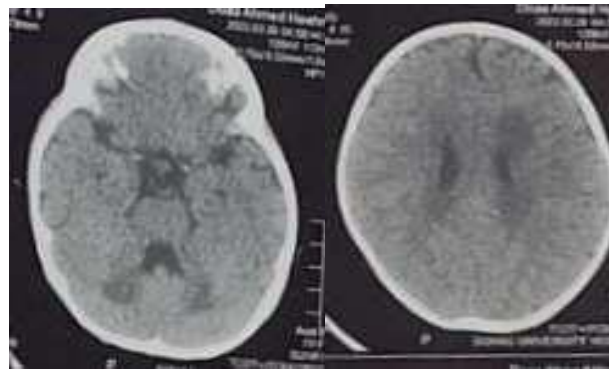


Figure 7 (A) and (B) axial T2W MRI images, (C) and (D) axial DWIs, (E) and (F) axial a FLAR showing brain stem, cerebellar vermis, both thalamic, both lentiform nuclei hyper signal intensities and restricted diffusion.

Case 5. Female child 1.5-year-old, diagnosed as MIS-C with neurological manifestations. CT and MRI findings suggest acute ischemic infarcts Vs cerebritis. (A), (B) and (C) axial CT images show hypodense areas at both cerebellar, corona radiata and centrum semi oval regions. (D), (E) and (F) axial T2W MRI images, (G), (H) and (I) axial DWIs, (J), (K) and (L) axial FLAR; showing hyper signal intensities, and restricted diffusion at these regions.



A

B



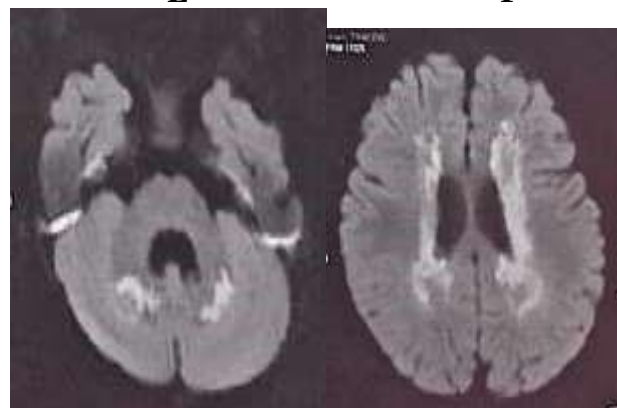
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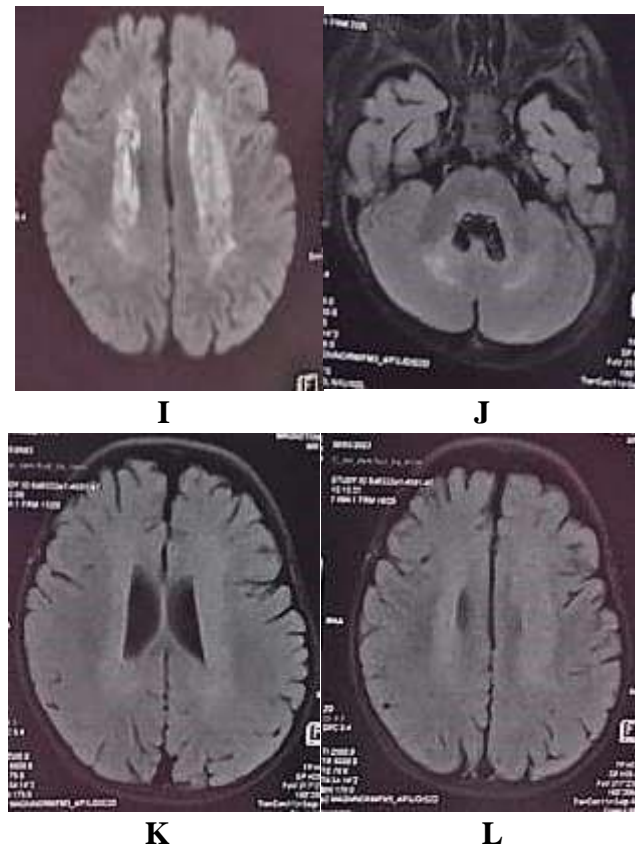


Figure 8 (A), (B) and (C) axial CT images show hypodense areas at both cerebellar, corona radiata and centrum semi oval regions. (D), (E) and (F) axial T2W MRI images, (G), (H) and (I) axial DWIs, (J), (K) and (L) axial FLAR; showing hyper signal intensities, and restricted diffusion at these regions.

Discussion:

MIS-C is defined as excessive immune response and inflammation following acute COVID-19 infection in children (12). Imaging findings of MIS-C associated with COVID-19 vary based on affected systems. Limited studies suggest nonspecific radiological findings with non-diagnostic criteria (8).

Neurological findings in children with COVID-19 and MIS-C may be caused by neuron damage, vascular injury, inflammation, and autoimmune damage (13).

Neurological manifestations in MIS-C include headache, confusion, and irritability. Severe manifestations like encephalopathy, seizures, coma, stroke, and meningitis are less common (14). Brain MRI is crucial for assessing neurologic deficits post MIS-C and guiding treatment decisions (9).

This study was performed on 25 patients with neurological symptoms out of 176 patients fulfill criteria of MIS-C (14%).

This is consistent with the results of a study conducted by LaRovere et al., (7) showed that 20% of 616 MIS-C patients had neurological symptoms. This also agrees with a study by Sandoval et al., (15) that reported out of 90 hospitalized children with SARS-CoV-2 infection, 14.4% (13 patients) had new-onset neurological symptoms.

In this study, patient's ages ranged from 3 months to 13 years with mean age 3.2 ± 10.716 years, 13 females and 12 males. This agrees with study done by Mihai et al., (16) that included 30 patients (boys and girls), aged 8 months to 15 years with no sex predominance.

According to general manifestations, the most common clinical presentations in our study were fever (96%), followed by circulatory shock and dyspnea (40% and 32% respectively), and the least common manifestation was skin rash (4%).

In a study by Cheung et al., (17), 17 patients were included. All had fever, 14 had gastrointestinal symptoms with most showing mucocutaneous findings, and 13 experienced shock. In another study done by Abdel-Mannan et al., (14), systemic manifestations included fever (n = 4), cardio-vascular shock (n = 4), rash (n = 4), and dyspnea (n = 2). All patients required mechanical ventilation and intensive care admission for cardiovascular shock (n = 4) and/or respiratory decompensation (n = 1). The neurological signs in our study were divided into central and peripheral signs, The most frequent central neurological signs were seizures (56%) and paresis (40%), followed by persistent headache and abnormal movements (12% for each). According to peripheral signs, the majority of children had muscle weakness and hyporeflexia (68%) and only one patient had visual changes (4%).

This agrees with a study by (Sandoval et al., (15) that revealed CNS symptoms: headache (61%), seizures (15.3%), encephalopathy (15.3%), pyramidal signs (7.6%). Peripheral nervous system symptoms: muscle weakness (61.5%), hypo/areflexia (23%), ageusia (15.3%), anosmia (7.6%). While a study done by Fink et al., (18) had shown headache (47%), acute encephalopathy (22%), dizziness (12%), and Anosmia (4%).

According to GCS, 32% came with mild brain injury (GCS 13-15), 40% with moderate injury (GCS 8-12), and 7 patients (28%) came with severe brain injury (GCS <8). Mean± SD was 11.16±8.13.

This disagrees with a study by Fink et al., (18) that revealed that 193 out of 205 patients came with mild brain injury (94.1%), while 4.9% came with moderate injury, and only 1% patients came with severe brain injury. This difference may be secondary to the lower number of cases in our study that came with neurological manifestations.

Brain CT was done in 22 patients (88%), the CT examinations were normal in 15 patients, and revealed brain alterations in seven (31.8%). In 6 patients, it revealed hypodensities (infarctions), and only in one case, it showed brain haemorrhage.

This agrees with study by Abbati et al., (19), where brain CT scans, performed in 11 patients (9%), revealed alterations in two (1.6%). In the first case, a 12-year-old boy with headache, dizziness, diplopia, and ataxia, it revealed an extensive hypodensity of the left cerebellum and some hypodense spots in the thalami; in the second one, a 10-month-old infant with MIS-C, with bulging anterior fontanelle and lethargy, it showed cerebral oedema and herniation.

Brain MRI was done in 15 patients (60%), the MRI examinations were normal in one case. The most common MRI findings were the nonspecific hyperintense signal in T2WI & FLAIR and restricted diffusion in DWI (80% and 73.3% respectively), followed by the ischemic infarctions that represent 47.7% of examined cases. The least common finding was the haemorrhage that was represented in one case. The most common affected sites were the corona radiata and centrum semi oval (24%), followed by lentiform nuclei (20%), then the occipital regions and corpus callosum (16%), then the brain stem, cerebellum and thalami (12%), and the least common sites were the internal capsule and the ventricles (4%).

A study done by Abdel-Mannan et al., (14), showed that all 4 patients with neurological signs had changes in the splenium of the corpus callosum (SCC). T2-hyperintense lesions with restricted diffusion were observed in 3 children. In the fourth patient, a splenial lesion with facilitated diffusion was detected. The genu was affected in 2 patients, while the centrum semi-ovale was involved bilaterally in 2 other patients.

In another study by Fenlon et al., (20) that examined 47 children with MIS-C, four of them underwent a brain MRI scan. Among these four children, one child had bilateral parieto-occipital cortical FLAIR MRI hyperintensity with restricted diffusion, mild cortical thickening and left centrum semi-ovale T2/FLAIR hyperintensity.

Furthermore, a case report by Abel et al., (21), showed a previously healthy child with MIS-C, who experienced reversible encephalopathy and restricted diffusion in the thalamic nuclei bilaterally without T2/FLAIR changes in brain MRI.

Main limitations of our study: single-center and small number of cases. Multicenter, multidisciplinary studies are needed to enhance knowledge in this area.

Conclusions:

CT and MRI imaging has vital role in children who were diagnosed as MIS-C and were presented with neurological symptoms involving both the central and peripheral nervous systems. These children in our study had CT and MRI brain imaging abnormalities, they were represented with different cerebral, cerebellar and brain stem lesions. Most of these lesions showed nonspecific hyperintense signal in T2WI and FLAIR and restricted diffusion in DWI by MRI examination as well as hypodense areas by CT examination. Haemorrhage is less common finding.

We recommend further research on a larger number of patients and a longer period of follow-up to confirm the findings.

List of abbreviations:

CT: computerized tomography

MRI: Magnetic resonance imaging

MIS-C: Multi Inflammatory Systemic Syndrome in children.

CDC: Centers for Disease Control

WHO: World Health Organization

GCS: Glasgow Coma Scale

PICU: Pediatric Intensive Care Unit

Declarations

Ethics approval and consent to participate.

The study approved by the Medical Research Ethics Committee of the Faculty of Medicine, Sohag University in Egypt. (Soh-Med-23-01-36). Informed consents were obtained from parents of patients included in the study.

Consent for publication

Parents of all participants included in the research gave written consent to publish the data obtained in this study. The authors agreed to publish the paper.

Availability of data and material

Data will be available upon request via contacting the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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No funding was obtained for this study.

Author contributions

AM conceived the study and designed it. YR and EM contributed equally to data collection and data analysis. The manuscript was written by AM and MA. Statistical analysis done by YR. All authors have read and approved the manuscript.

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