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Neuroimaging Spectrum of Multisystem Inflammatory Syndrome in Children (MIS-C) Related to COVID-19: A Comprehensive Review

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ABSTRACT

Background: Multisystem inflammatory syndrome in children (MIS-C) emerged as a severe post–SARS-CoV-2 hyperinflammatory condition with frequent neurological involvement ranging from headache and encephalopathy to rare cerebrovascular events. Although clinical criteria established by WHO, CDC, and RCPCH facilitate recognition, neuroimaging has become pivotal for characterizing central nervous system (CNS) injury, refining differential diagnoses, guiding acute management, and informing prognosis. MRI consistently reveals a heterogeneous spectrum that includes reversible splenial lesions of the corpus callosum (RESLES/CLOCC), ADEM-like demyelinating patterns, posterior reversible encephalopathy syndrome (PRES), microvascular injury with microhemorrhages, ischemic infarction, and occasional hemorrhagic/necrotizing encephalopathy. The radiologic heterogeneity mirrors the interplay of endothelial dysfunction, cytokine-driven neuroinflammation, and hypercoagulability more than direct neurotropism, as viral RNA is infrequently detected in cerebrospinal fluid. This review synthesizes current evidence on the neuroimaging spectrum of MIS-C associated with COVID-19, emphasizing practical, radiology-first insights. We delineate core MRI and CT patterns, highlighting sequence-specific hallmarks on DWI/ADC, FLAIR, SWI, and post-contrast imaging; correlate imaging phenotypes with proposed mechanisms, including cytokine-mediated permeability, immune-mediated demyelination, endothelialitis, and thromboinflammation; outline prognostic implications—particularly the adverse significance of diffusion restriction and hemorrhage versus the typically favorable trajectory of RESLES and PRES; present a structured differential diagnosis tailored to the pandemic context (viral encephalitis, classic ADEM, Kawasaki disease spectrum, autoimmune and metabolic mimics); and propose pragmatic imaging pathways for acute assessment and follow-up in children with suspected or confirmed MIS-C. Neuroimaging is central to the multidisciplinary care of MIS-C, with MRI providing sensitive biomarkers of disease mechanism and outcome. Recognition of signature patterns—cytotoxic splenial lesions, multifocal non-confluent white-matter hyperintensities, ADEM-like changes, PRES, microhemorrhages, and ischemia—supports timely immunomodulatory therapy and targeted supportive care. Diffusion restriction and hemorrhagic components portend poorer neurological recovery, whereas reversible vasogenic and splenial changes generally resolve. Standardized pediatric MRI protocols that consistently include DWI/ADC, FLAIR, and SWI, coupled with scheduled follow-up at 3–6 months for moderate-to-severe cases, can stratify risk and guide rehabilitation. Future priorities include harmonized imaging criteria across definitions, integration of imaging with immunophenotyping and endothelial biomarkers, and prospective studies to clarify long-term neurodevelopmental outcomes and optimize imaging-based prognostication in MIS-C.

Keywords: *Neuroimaging, Multisystem Inflammatory Syndrome, COVID-19*

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019 and the subsequent declaration of a global pandemic reshaped pediatric infectious disease paradigms, not only because children generally experience milder respiratory illness than adults, but also due to distinct age-related host responses that modulate disease expression. Differences in renin–angiotensin system biology—particularly ACE2 receptor distribution and function—together with developmental immunology are thought to underlie this dissociation in severity profiles between age groups. Early pediatric cohorts emphasized mild or asymptomatic infection; however, accumulating data have clarified that “mild” does not equate to “benign,”

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especially when extrapulmonary systems, including the nervous system, are considered. These observations set the stage for a focused evaluation of neuro-COVID in children and, specifically, of the neuroimaging correlates that inform diagnosis, monitoring, and prognosis. [1,2]

Multiple, non–mutually exclusive mechanisms have been proposed to explain neurological involvement in pediatric COVID-19. Putative routes of neuroinvasion include transcribriform spread via the olfactory epithelium, axonal transport along cranial nerves, leukocyte-facilitated entry across a disrupted blood–brain barrier, and endothelial infection with secondary parenchymal injury. Parallel systemic processes—hyperinflammation, endothelialitis, and coagulopathy—can indirectly precipitate encephalopathy, ischemia, or microhemorrhage without demonstrable viral RNA in cerebrospinal fluid. Experimental models and early clinico-radiologic series collectively suggest that indirect, immune-mediated and vascular pathways dominate in children, while direct neurotropism appears less common, a distinction with important implications for imaging interpretation and therapeutic targeting. [2–4]

The pediatric landscape changed dramatically with recognition of multisystem inflammatory syndrome in children (MIS-C), a post-infectious hyperinflammatory condition temporally linked to SARS-CoV-2 exposure. Although initial pediatric COVID-19 was often labeled "mild," MIS-C highlighted the capacity for severe, systemic illness with notable neurological morbidity ranging from headache and altered mental status to seizures, encephalitis/encephalopathy, and occasional cerebrovascular events. Case series and observational studies rapidly cataloged extracardiac and neurologic findings, revealing a heterogeneous spectrum that overlaps with, yet is pathophysiologically distinct from, acute SARS-CoV-2 infection. For radiologists, the challenge is to recognize imaging patterns—particularly on MRI—that suggest MIS-C–related neuroinflammation and to differentiate them from mimics such as primary demyelination or viral encephalitis. [5,6]

Despite rapid advances, key knowledge gaps persist at the interface of pediatric neurology and radiology. The true incidence of CNS involvement in MIS-C is variably reported, reflecting differences in surveillance intensity, imaging protocols, and diagnostic thresholds. Correlation between neuroimaging phenotypes (e.g., reversible splenial lesions, ADEM-like patterns, PRES, microvascular injury) and clinical outcomes remains incompletely defined, as do optimal follow-up intervals and prognostic biomarkers. This review aims to synthesize current evidence on the neuroimaging spectrum of MIS-C, integrate pathophysiological context, and outline a pragmatic imaging approach that aligns with contemporary pediatric practice. We also highlight research priorities, including standardized MRI protocols, harmonized outcome measures, and mechanistic studies linking imaging to immunophenotypes and endothelial dysfunction. [7,8]

MIS-C Definitions

Multisystem inflammatory syndrome in children (MIS-C) is a post-infectious hyperinflammatory condition temporally associated with SARS-CoV-2 infection and has become one of the most significant pediatric complications of the COVID-19 pandemic. To establish diagnostic clarity, multiple professional bodies including the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the Royal College of Paediatrics and Child Health (RCPCH) have published criteria to define MIS-C. These definitions share common ground by emphasizing persistent fever, systemic inflammation, multisystem involvement, and evidence of prior or recent SARS-CoV-2 exposure. However, subtle differences in thresholds, organ system emphasis, and laboratory parameters have introduced heterogeneity in case identification and epidemiological reporting across studies [9,10].

The WHO criteria define MIS-C in patients aged 0–19 years presenting with fever for at least three days, accompanied by at least two clinical features such as mucocutaneous signs, hemodynamic instability, cardiac dysfunction, coagulopathy, or gastrointestinal symptoms. Laboratory confirmation of systemic inflammation is required, along with exclusion of alternative microbial etiologies. A critical element is the demonstration of SARS-CoV-2 exposure or infection within the preceding weeks, determined by RT-PCR, serology, or antigen testing. These criteria emphasize the broad systemic nature of the syndrome and help standardize diagnosis internationally, particularly in low-resource settings where the full spectrum of laboratory and imaging modalities may not be available [11].

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The CDC criteria apply to children under 21 years of age and require fever lasting at least 24 hours, evidence of systemic inflammation, and involvement of at least two organ systems, which may include cardiac, gastrointestinal, dermatological, hematological, respiratory, renal, or neurological domains. The CDC also highlights the importance of excluding other plausible diagnoses and mandates laboratory or epidemiological evidence of recent SARS-CoV-2 infection or exposure within four weeks prior to symptom onset. This broader time frame allows for the recognition of MIS-C cases with delayed immune dysregulation. The CDC framework further incorporates laboratory abnormalities such as lymphopenia, neutrophilia, hypoalbuminemia, and elevated inflammatory markers, which reflect the hyperinflammatory state seen in MIS-C [12].

The RCPCH criteria emphasize persistent fever with single or multi-organ dysfunction, often manifesting as shock, hypoxia, or cardiac involvement, with concurrent laboratory evidence of systemic inflammation. Unlike the CDC and WHO, the RCPCH does not require laboratory confirmation of SARS-CoV-2 infection, reflecting early recognition of the syndrome during the pandemic when testing availability was limited. The inclusion of clinically suspected but laboratory-negative cases acknowledges the diagnostic challenges posed by variable viral detection windows and reinforces the importance of clinical correlation. Patients frequently demonstrate mucocutaneous and gastrointestinal features in addition to cardiovascular dysfunction, with many requiring hospitalization and intensive care support [13].

Although there is significant overlap among the three diagnostic frameworks, their subtle differences have practical implications. For example, the WHO requires a minimum fever duration of three days, while the CDC considers 24 hours sufficient. Similarly, the RCPCH allows for diagnosis without laboratory evidence of SARS-CoV-2, which broadens case ascertainment but potentially increases heterogeneity. In research and clinical practice, these discrepancies affect reported incidence rates, severity classifications, and the comparability of international cohorts. Consequently, epidemiological studies have reported variable prevalence and outcome data, underscoring the need for harmonization of diagnostic standards. Recent efforts have highlighted the importance of integrating elements from all three definitions to ensure timely recognition while preserving diagnostic specificity [14].

MIS-C definitions continue to evolve as more is learned about the syndrome's clinical spectrum and its overlap with conditions such as Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. Importantly, radiologists and neurologists must be familiar with these definitions because neuroimaging findings often represent key pieces of evidence for multisystem involvement. Brain imaging abnormalities, when coupled with systemic features, can tip the balance toward early diagnosis in ambiguous cases. Thus, diagnostic frameworks not only serve epidemiological purposes but also provide guidance for interdisciplinary teams managing these critically ill children [15].

Neurological Manifestations of SARS-CoV-2 with MIS-C

Neurological involvement is increasingly recognized as an important component of MIS-C, with clinical manifestations ranging from mild nonspecific symptoms to severe and potentially life-threatening complications. Early reports of pediatric COVID-19 often emphasized respiratory or gastrointestinal features, but accumulating evidence has demonstrated that neurological presentations are both frequent and diverse. Children affected by MIS-C may develop neurological complications as a direct effect of viral exposure, as part of the systemic inflammatory cascade, or through secondary consequences such as hypoxia, coagulopathy, and vascular injury. Epidemiological data vary considerably, reflecting differences in diagnostic vigilance and case definitions, but studies consistently highlight that neurological symptoms are present in a significant proportion of pediatric MIS-C cases [16,17].

Incidence rates of neurological involvement show geographical variability. A large multicenter cohort in the United States identified severe neurological complications in approximately 5% of hospitalized MIS-C cases, while an Italian study employing systematic neurological evaluation reported neurological manifestations in up to 93% of patients. Within the Italian cohort, 68% demonstrated mild or nonspecific symptoms such as headache and irritability, while 26% had moderate-to-severe manifestations including encephalopathy, seizures, and focal deficits. Importantly, the majority of these patients responded favorably to immunomodulatory therapy,

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supporting the hypothesis of an inflammatory rather than primarily infectious mechanism underlying neurological disease in MIS-C [18].

Clinical Spectrum

The clinical spectrum of neurological manifestations in MIS-C is broad and encompasses both nonspecific and specific findings. Headache is among the most frequently reported symptoms, occurring in 37–68% of cases, followed by fatigue, myalgias, irritability, and dizziness. While often considered benign, these symptoms may precede more significant neurological involvement. Less common manifestations include circadian rhythm disturbances, photophobia, and mood or behavioral changes, which may reflect underlying encephalopathy. In severe cases, children present with altered consciousness, seizures, focal neurological deficits, or neuropsychiatric disturbances such as delirium. The heterogeneity of presentations poses diagnostic challenges, especially in younger children where symptom reporting may be limited [19,20].

Encephalitis and Encephalopathy

Among the most concerning neurological complications of MIS-C are encephalopathy and encephalitis. Younger children, particularly those around 5–6 years of age, appear especially vulnerable to these presentations. Clinically, they may present with confusion, lethargy, irritability, mood changes, or seizures. Electroencephalography often reveals generalized slowing, consistent with diffuse cerebral dysfunction. MRI findings are variable but include cytotoxic lesions of the corpus callosum (CLOCC), acute disseminated encephalomyelitis (ADEM)-like lesions, or signal abnormalities in the thalami and brainstem. Immunological studies have occasionally identified autoantibodies against neural antigens, further implicating an autoimmune-mediated process. Treatment with high-dose corticosteroids and intravenous immunoglobulin (IVIG) has shown favorable responses in many reported cases, underscoring the importance of early recognition [21].

Cerebellitis

Cerebellar involvement, although rare, has been described in MIS-C. Children may present with acute ataxia, dysarthria, nystagmus, and titubation. Neuroimaging may reveal signal changes within the cerebellar hemispheres, although cerebrospinal fluid analysis is often unremarkable. Corticosteroid therapy generally results in clinical improvement, suggesting an inflammatory basis rather than direct viral cytopathic effect. These cases illustrate the heterogeneity of CNS involvement and highlight the importance of considering MIS-C in pediatric patients presenting with acute cerebellar syndromes during the pandemic era [22].

Delirium and Neuropsychiatric Features

Adolescents with MIS-C may exhibit neuropsychiatric complications, with delirium being a particularly well-documented feature. Delirium in these patients is characterized by fluctuating attention, impaired cognition, and psychotic symptoms. The presence of delirium complicates management, often requiring multidisciplinary care that incorporates both neurological and psychiatric expertise. The pathophysiological basis is believed to be related to systemic inflammation, cytokine dysregulation, and blood-brain barrier compromise rather than primary psychiatric disease. Recognizing this phenomenon is essential for early intervention and to avoid misattributing symptoms to psychosomatic causes [23].

Cerebrovascular Complications

Although uncommon, cerebrovascular events such as arterial ischemic stroke have been reported in children with MIS-C, with an estimated incidence of around 0.2%. Clinical presentations include hemiparesis, aphasia, or altered consciousness, and imaging often reveals large-vessel occlusions. The underlying mechanism is thought to involve hypercoagulability, endothelial dysfunction, and systemic vasculitis induced by the hyperinflammatory response. Early anticoagulation in conjunction with immunomodulatory therapy is crucial to improving outcomes in these patients. The rarity but severity of these events underscores the importance of vigilant neurological monitoring in MIS-C [24].

Pseudotumor Cerebri and Intracranial Hypertension

Another rare but notable manifestation is pseudotumor cerebri, or idiopathic intracranial hypertension, characterized by papilledema and elevated cerebrospinal fluid pressure despite normal neuroimaging. The mechanism is hypothesized to involve cytokine-mediated alterations in cerebrospinal fluid dynamics. Treatment

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strategies may include acetazolamide or repeated lumbar punctures in addition to standard MIS-C therapies, with most patients achieving favorable outcomes when promptly managed [22].

Cranial Neuropathies

Isolated cranial nerve palsies have also been documented, particularly involving the oculomotor nerve. Children may present with ptosis, ophthalmoplegia, and pupillary abnormalities. Cerebrospinal fluid analysis often reveals albuminocytologic dissociation, a finding consistent with post-infectious immune-mediated neuropathy. While these cases are rare, they highlight the spectrum of peripheral nervous system involvement in MIS-C and further support the hypothesis of immune-mediated injury rather than direct viral invasion [25].

Therapeutic Considerations

The favorable response of most neurological manifestations in MIS-C to immunomodulatory therapies strongly supports an inflammatory pathogenesis. Standard treatment typically involves IVIG in combination with corticosteroids, with adjunctive therapies such as anticonvulsants for seizure control, anticoagulation for thrombotic events, and acetazolamide for intracranial hypertension. Early recognition of neurological involvement and initiation of therapy are critical to improving outcomes and preventing long-term sequelae. These therapeutic observations also serve as indirect evidence of the immunological rather than infectious basis of MIS-C-related neurological disease [19,20].

Pathophysiology

The neurological complications associated with MIS-C represent the culmination of multiple converging mechanisms, including direct viral interactions with neural tissue, systemic vascular injury, exaggerated inflammatory responses, and autoimmune cross-reactivity. Understanding these mechanisms is essential for interpreting neuroimaging findings, as different pathways of injury may manifest as distinct radiological patterns. While direct viral neurotropism was initially suspected to play a dominant role, subsequent studies have emphasized that most neurological symptoms in MIS-C are likely mediated indirectly through inflammation, immune dysregulation, and vascular dysfunction rather than active viral replication within the central nervous system [26].

Viral Entry and Neural Vulnerability

SARS-CoV-2 primarily exploits angiotensin-converting enzyme 2 (ACE2) receptors and the transmembrane protease serine 2 (TMPRSS2) for cellular entry. Both proteins are expressed in central nervous system tissues, although their distribution varies by age and neural region. The olfactory bulb and neuroepithelium, where ACE2 expression is relatively high, are potential entry points for the virus, explaining reports of anosmia and providing a plausible route for direct neural invasion. However, the rarity of viral RNA detection in cerebrospinal fluid samples from affected children suggests that direct infection of the CNS is not the predominant mechanism. Instead, these pathways may serve as permissive entry points that initiate downstream immune cascades, contributing to indirect neurological damage [27].

Direct Neural Injury

Experimental models of coronavirus infection provide evidence for direct transcribriform penetration of the olfactory nerve, with subsequent neural dissemination through retrograde axonal transport. This theoretical model aligns with the clinical observation of anosmia and certain focal neurological deficits in COVID-19 patients. Other possible mechanisms include trans-synaptic propagation along cranial nerves, migration of infected leukocytes across a compromised blood-brain barrier, and direct endothelial infection of cerebral microvasculature. Despite these possibilities, the majority of pediatric MIS-C cases lack virological confirmation of direct CNS invasion, which shifts emphasis toward alternative mechanisms such as immune-mediated injury [28].

Vascular Pathogenesis

Vascular involvement plays a central role in MIS-C pathophysiology, given the established interactions between SARS-CoV-2 and endothelial ACE2 receptors. Viral binding can induce endothelial inflammation, disrupt the integrity of the vascular barrier, and precipitate a cascade of coagulation abnormalities. These changes

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predispose to vasculitis, cerebral autoregulation failure, microthrombosis, and large-vessel occlusion, each of which may be detected radiologically as ischemic infarcts or microhemorrhages. Children with MIS-C frequently demonstrate elevated D-dimer levels and other coagulopathy markers, correlating with the observed risk of cerebrovascular events such as stroke and intracranial hemorrhage [29].

Neuroinflammatory Mechanisms

MIS-C is primarily regarded as a hyperinflammatory syndrome with cytokine-mediated pathology. Distinct cytokine signatures—including elevated interleukin (IL)-1β, IL-6, IL-17, and interferon-γ—have been reported in affected patients. These proinflammatory mediators disrupt blood-brain barrier integrity, activate microglia, and interfere with normal astrocytic and endothelial signaling. The net effect is increased vascular permeability, leukocyte infiltration, and subsequent white matter injury, which can be visualized on MRI as demyelination, cytotoxic lesions, or diffuse white matter hyperintensities. These mechanisms explain why neuroimaging findings in MIS-C often resemble post-infectious demyelinating syndromes rather than direct viral encephalitis [30,31].

Autoimmune Considerations

Autoimmune cross-reactivity is another plausible mechanism underlying neurological involvement in MIS-C. Structural similarities between viral proteins and host neural antigens such as myelin basic protein, S100B, and gangliosides may trigger autoantibody production through molecular mimicry. This mechanism provides a basis for conditions like Guillain-Barré syndrome, cranial neuropathies, and post-infectious demyelinating lesions observed in pediatric COVID-19 cases. Importantly, the absence of worsening disease in patients receiving convalescent plasma argues against antibody-dependent enhancement as a major driver, suggesting that targeted autoimmunity rather than generalized antibody activity contributes to neurological sequelae [32].

Developmental Considerations

Pediatric neurodevelopmental factors also play a role in determining susceptibility to neurological injury from MIS-C. Age-dependent differences in blood-brain barrier maturation, microglial phenotypes, and neurovascular unit development may influence both vulnerability to injury and the specific radiological manifestations observed. For example, incomplete myelination in younger children could make white matter more susceptible to inflammatory damage, leading to imaging patterns that resemble ADEM or cytotoxic splenial lesions. These developmental considerations help explain why pediatric patients often present with different neurological patterns compared to adults with COVID-19 [33].

Diagnostic and Therapeutic Implications

Clinically, the observation that cerebrospinal fluid viral RNA is rarely detected despite frequent neurological symptoms supports an immune-mediated rather than virological model of CNS involvement. The correlation between elevated inflammatory markers and the severity of neurological complications further reinforces this interpretation. From a therapeutic perspective, the consistent clinical improvement following immunomodulatory therapy (IVIG and corticosteroids) provides additional indirect evidence of inflammatory pathogenesis. Nevertheless, unanswered questions remain regarding optimal diagnostic strategies to confirm CNS involvement, long-term cognitive outcomes in children with MIS-C-related neuroimaging abnormalities, and the potential role of age-specific treatment protocols. These knowledge gaps highlight the importance of multidisciplinary research integrating radiology, neurology, immunology, and pediatric critical care [34].

Severe Neurological Complications and Risk Groups

Severe neurological complications in MIS-C are frequently observed among hospitalized children, particularly those requiring intensive care. Acute encephalopathy, seizures, and delirium are the most common serious presentations, often associated with prolonged hospitalization and the need for multidisciplinary management. These complications substantially increase the risk of new functional impairments at discharge, including motor, cognitive, and behavioral deficits, highlighting the long-term impact of MIS-C beyond the acute illness [35].

Two primary pediatric risk groups appear most vulnerable. The first includes children with preexisting neurological disorders, who demonstrate higher susceptibility to severe outcomes when infected with SARS-CoV-2. The second group comprises previously healthy children who develop MIS-C but experience acute

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neurological complications due to the overwhelming inflammatory and vascular response. Within both groups, thrombocytopenia has been noted as a potential prognostic marker, correlating with the severity of neurological involvement and worse outcomes [36].

These observations underscore the need for systematic neurological assessment in all children hospitalized with MIS-C or COVID-19, irrespective of baseline health status. Long-term follow-up and rehabilitative strategies are essential for affected children, echoing the structured care models used in post-intensive care syndromes. Recognition of high-risk populations allows early intervention and better allocation of resources to prevent chronic neurological sequelae [37].

Imaging Findings in MIS-C

Imaging plays a pivotal role in the evaluation of MIS-C, given the syndrome's ability to mimic other pediatric inflammatory or infectious diseases. While thoracic, cardiac, and abdominal imaging provide important systemic context, neuroimaging constitutes the most critical domain due to the frequency, diversity, and prognostic importance of neurological manifestations. Radiologists are thus central to both initial recognition and longitudinal follow-up of MIS-C, where subtle imaging clues may dictate clinical management and outcome predictions [38].

Thoracic Imaging

Chest radiographs in MIS-C frequently reveal peribronchial thickening, perihilar prominence, and variable pleural effusions. Unlike acute pediatric COVID-19, which often demonstrates diffuse bilateral ground-glass opacities, MIS-C imaging more commonly reflects cardiac dysfunction and systemic inflammation. Thoracic CT scans may show atelectasis, consolidations, or interlobular septal thickening, occasionally with bilateral effusions. These findings, though nonspecific, gain diagnostic value when integrated with extracardiac abnormalities and the clinical context of systemic inflammation [39].

Cardiac Imaging

Cardiac involvement is present in nearly one-third of MIS-C cases and is a major determinant of morbidity. Echocardiography typically reveals left ventricular dysfunction, coronary artery dilatation, or pericardial effusion. Cardiac MRI further characterizes myocardial injury, demonstrating edema and inflammation on T2-weighted and T1 mapping sequences. Late gadolinium enhancement, indicative of fibrosis, is uncommon, suggesting that MIS-C cardiac pathology is more often reversible compared to classic viral myocarditis. Recognizing cardiac abnormalities is essential because cardiac dysfunction may exacerbate neurological complications through reduced cerebral perfusion and systemic hypoxia [40,41].

Abdominal Imaging

Abdominal CT and ultrasound often reveal gallbladder wall thickening, mesenteric lymphadenopathy, bowel wall thickening, hepatosplenomegaly, or ascites. These findings frequently mimic appendicitis or other surgical emergencies, complicating management in the acute setting. Vascular complications such as inferior vena cava or portal vein thrombosis are occasionally detected and underscore the prothrombotic milieu of MIS-C. While primarily systemic in implication, abdominal imaging contributes to the recognition of MIS-C as a multisystem disease and differentiates it from isolated neurological or respiratory illnesses [42,43].

Neurological Imaging

Neurological involvement is among the most clinically significant aspects of MIS-C, with radiological abnormalities reported in nearly two-thirds of affected children with neurological symptoms. MRI is the primary modality due to its superior sensitivity in detecting white matter, cortical, and vascular changes. CT is generally reserved for acute evaluation of hemorrhage or infarction, or in settings where MRI is unavailable. The neuroimaging spectrum can be grouped into several characteristic patterns that correspond with underlying pathophysiological mechanisms [44].

1. White Matter Abnormalities

Multifocal, non-confluent hyperintense white matter lesions on FLAIR and T2-weighted MRI are the most frequent abnormalities. These lesions typically involve periventricular and subcortical regions and may appear symmetrically or asymmetrically. While many resolve with treatment, persistent lesions have been documented

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in longitudinal follow-up, raising concern for long-term cognitive or developmental sequelae. The variability in outcomes highlights the need for standardized imaging follow-up protocols to monitor lesion evolution [45,46].

2. Corpus Callosum Lesions (RESLES/CLOCC)

Reversible splenial lesion syndrome (RESLES), characterized by transient diffusion-restricted lesions in the splenium of the corpus callosum, has emerged as a hallmark finding in MIS-C. These cytotoxic lesions are thought to result from inflammatory cytokine storms causing intramyelinic edema and excitotoxic injury. They are generally reversible and associated with favorable outcomes, but their recognition is important for differentiating MIS-C from conditions such as acute disseminated encephalomyelitis (ADEM) or viral encephalitis [47].

3. Inflammatory and Demyelinating Patterns

ADEM-like presentations are characterized by multifocal white and gray matter lesions involving the cerebral hemispheres, basal ganglia, thalami, and brainstem. These lesions often enhance with gadolinium, reflecting active demyelination or inflammation. Some cases demonstrate myelitis, with longitudinally extensive cord lesions or nerve root enhancement consistent with Guillain-Barré syndrome. Such findings reinforce the immune-mediated pathophysiology of MIS-C and have important implications for therapy, as they respond well to corticosteroids and IVIG [48].

4. Ischemic and Hemorrhagic Events

The hypercoagulable state of MIS-C predisposes to vascular injury. Ischemic infarctions, particularly large-vessel occlusions, have been described, manifesting radiologically as restricted diffusion and cortical/subcortical infarcts. Hemorrhagic manifestations include microhemorrhages, cortical petechiae, and, in rare cases, acute hemorrhagic necrotizing encephalopathy. These events correlate strongly with poor outcomes, as ischemia and hemorrhage are less reversible than inflammatory lesions. Susceptibility-weighted imaging (SWI) is particularly valuable for detecting microhemorrhages and should be included in pediatric MIS-C protocols [49].

5. Posterior Reversible Encephalopathy Syndrome (PRES)

PRES, characterized by vasogenic edema in the parieto-occipital regions, has been observed in MIS-C, often in the context of hypertension, systemic inflammation, or endothelial dysfunction. MRI demonstrates hyperintense T2/FLAIR signals without diffusion restriction, consistent with reversible edema. Early recognition is critical, as PRES is reversible with blood pressure and inflammation control, whereas delayed treatment may lead to permanent cortical damage [50].

6. Advanced MRI Techniques

Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps are crucial for distinguishing cytotoxic edema (seen in ischemia and CLOCC) from vasogenic edema (seen in PRES). MR spectroscopy has revealed metabolic changes such as elevated choline and reduced N-acetylaspartate in affected regions, indicating membrane turnover and neuronal injury. Diffusion tensor imaging (DTI) and functional MRI may provide future insights into subtle white matter connectivity and cognitive outcomes, though these remain primarily research tools at present [51].

Prognostic Implications and Evolution of Findings

Longitudinal studies show two major trajectories: reversible changes, such as RESLES and mild white matter lesions, which resolve completely; and irreversible sequelae, such as encephalomalacia, myelomalacia, or cortical atrophy, which persist and are associated with cognitive or motor impairment. Diffusion restriction on MRI, particularly in ischemic lesions, has been identified as a strong predictor of poor prognosis. Conversely, non-confluent white matter hyperintensities often resolve, correlating with more favorable outcomes. Recognizing these prognostic markers allows radiologists to contribute directly to clinical risk stratification and long-term planning [46,52].

Prognostic Implications and Evolution of Neuroimaging Findings

The prognostic value of neuroimaging in MIS-C lies in its ability to differentiate between reversible inflammatory changes and irreversible structural injury. Early recognition of these imaging patterns enables

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timely therapeutic intervention and helps predict long-term neurological outcomes. The diverse radiological manifestations observed in MIS-C reflect the interplay between systemic inflammation, vascular injury, and immune-mediated demyelination, with outcomes that vary considerably depending on the dominant mechanism at play [53].

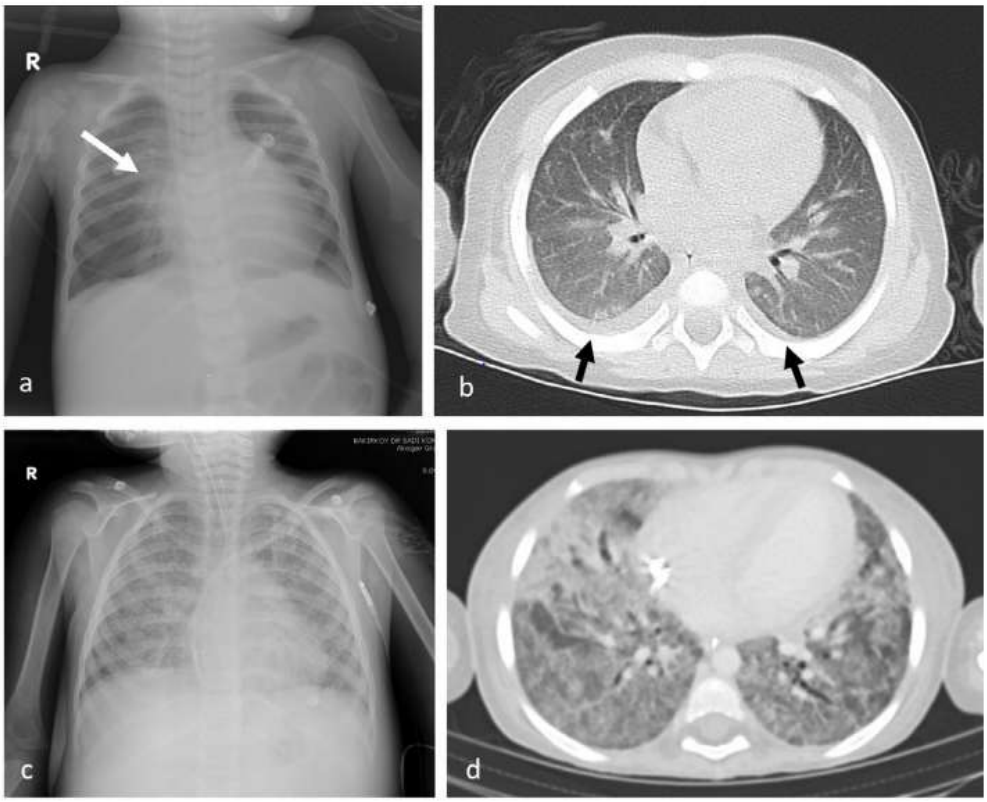

Fig 1. A chest X-ray of a 2-year-old boy reveals perihilar opacity and peribronchial thickening, indicated by a white arrow (a). In another case, a thoracic CT scan of a 23-month-old girl displays bilateral pleural effusion, marked by black arrows (b). Additionally, imaging of a 4-year-old girl shows bilateral diffuse opacities, ground-glass densities, and consolidation on both chest X-ray and thoracic CT (c, d) [66].

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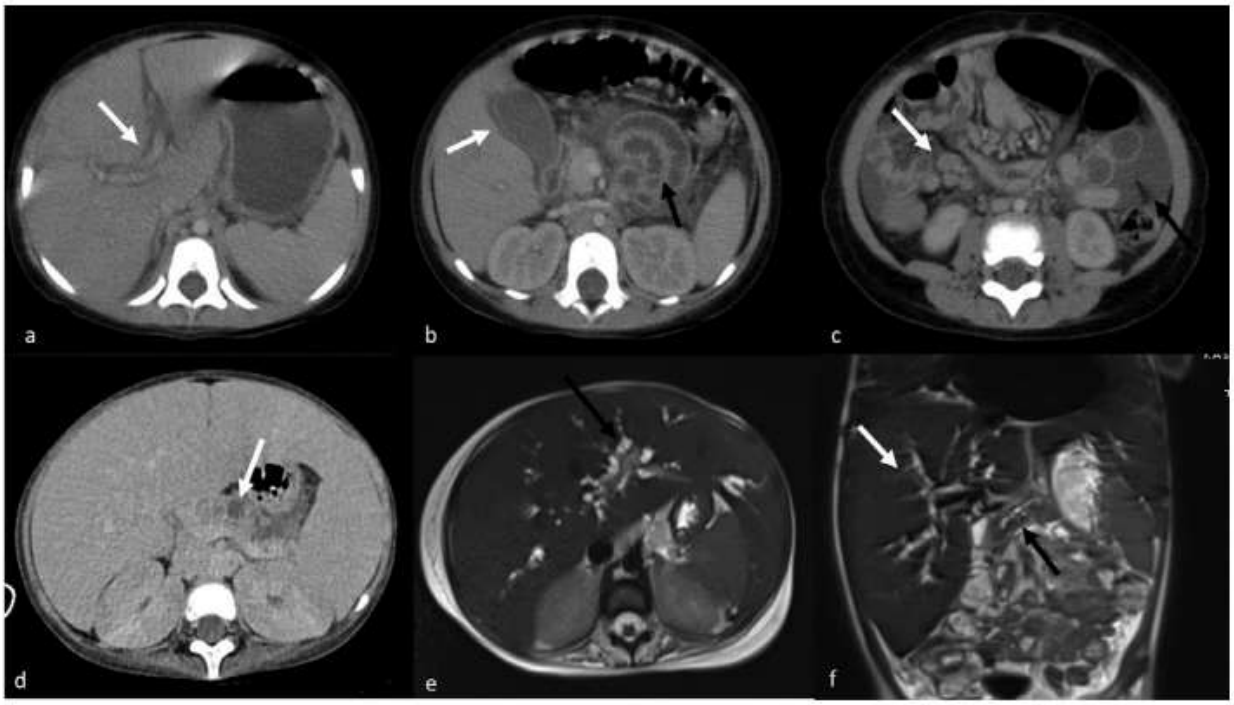

Fig 2. Abdominal CT scans of a 23-month-old girl demonstrate periportal edema (white arrow, *a*), gallbladder edema (white arrow), and intestinal wall thickening (black arrow, *b*). Additional findings include multiple lymph nodes in the right lower quadrant (white arrow) and free fluid (black arrow, *c*). In a 4-year-old female, an abdominal CT reveals pancreatic atrophy, heterogeneous parenchyma, and necrotic regions (white arrow, *d*). MRCP images of the same child show dilated intrahepatic bile ducts and an enlarged main pancreatic duct (e, f) [66].

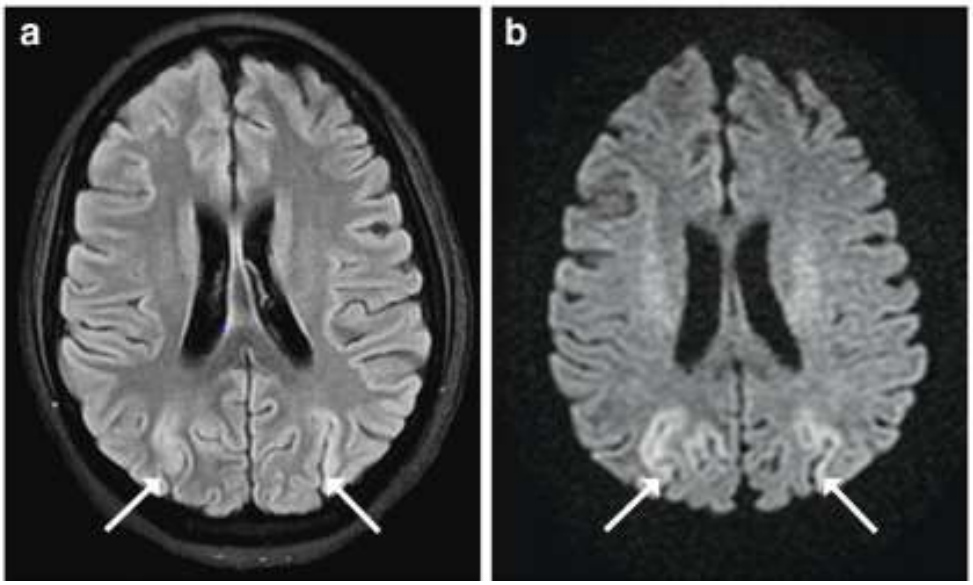

Fig 3. A 14-year-old girl initially presented with classic multisystem inflammatory syndrome in children (MIS-C) symptoms, including fever, abdominal pain, and myocardial dysfunction, alongside a positive COVID-19 serology. During hospitalization, she developed thrombotic microangiopathy with hemolytic anemia and altered mental status. Brain imaging findings: **a, b**: Axial FLAIR MRI (*a*) and corresponding diffusion-weighted imaging (*b*) at the level of the lateral ventricles and corona radiata reveal bilateral parieto-occipital cortical FLAIR hyperintensity with restricted diffusion, along with mild cortical thickening (arrows).[67].

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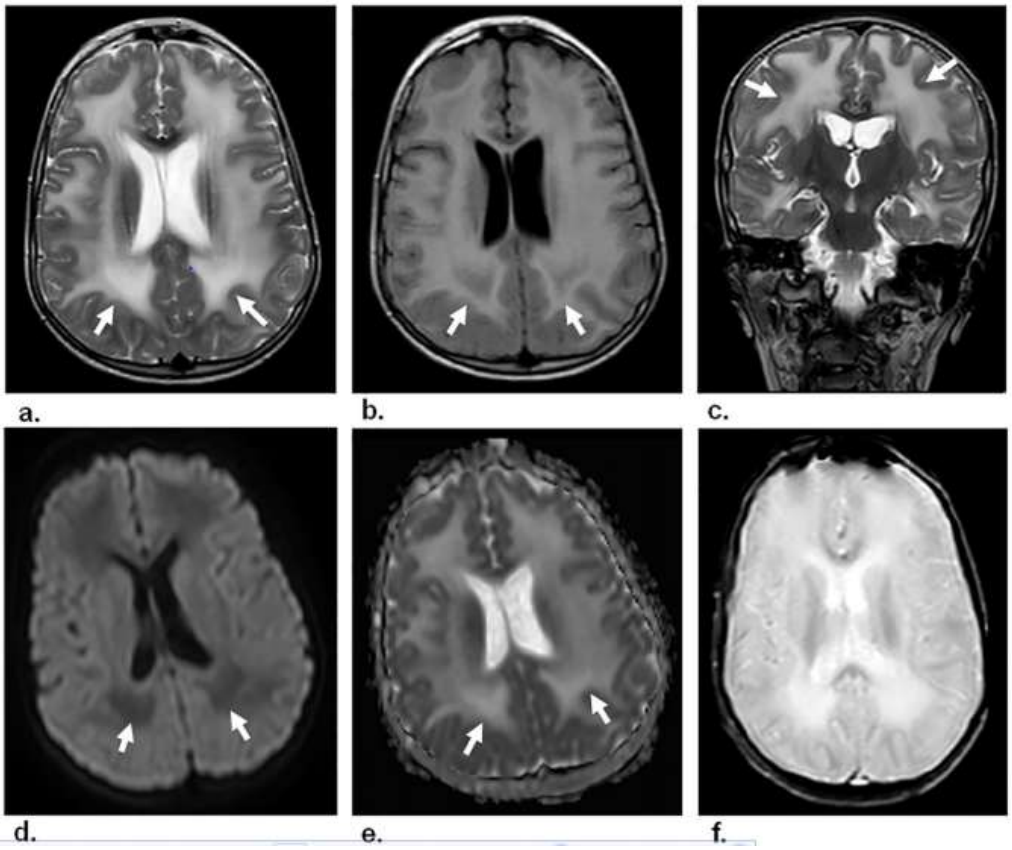

Fig 4. An 11-year-old boy with acute COVID-19 infection presented with fever, cough, and encephalopathy. (a) Axial T2W and (b) Axial FLAIR images demonstrate extensive, confluent white matter hyperintensities (arrows). (c) Coronal T2W imaging confirms these abnormalities (arrows). (d) DWI and (e) ADC map reveal no restricted diffusion (arrows). (f) Axial T2*W image shows no evidence of hemorrhage [67].

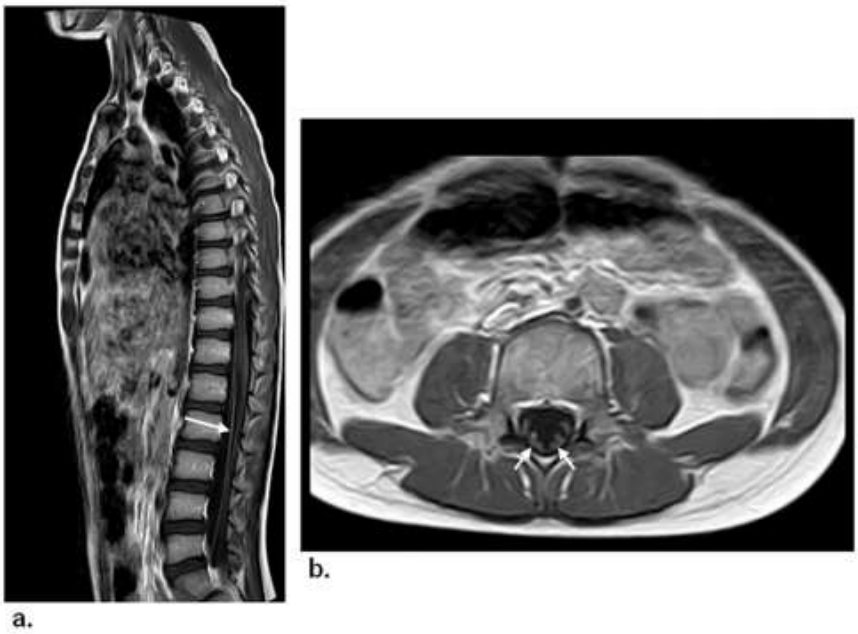

Fig 5. A 6-year-old boy diagnosed with MIS-C exhibited fever, diarrhea, and flaccid paralysis. Post-contrast MRI demonstrated:(a) Sagittal and (b) Axial T1-weighted images showing abnormal enhancement of the cauda equina nerve roots (arrows) [67].

Reversible Changes

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A substantial proportion of neuroimaging abnormalities in MIS-C demonstrate reversibility, particularly cytotoxic lesions of the corpus callosum (CLOCC/RESLES), mild white matter hyperintensities, and posterior reversible encephalopathy syndrome (PRES). These lesions often resolve completely within weeks to months following immunomodulatory therapy and supportive care. The reversibility of these findings supports the hypothesis that transient metabolic and inflammatory insults, rather than permanent neuronal destruction, underlie their pathophysiology. Recognizing these imaging patterns provides reassurance to clinicians and families and underscores the importance of early treatment to limit progression [54].

Irreversible Sequelae

Conversely, children with ischemic infarctions, hemorrhagic lesions, or severe necrotizing encephalopathy frequently develop long-term sequelae. These include encephalomalacia, myelomalacia, cortical thinning, and gliosis, which persist on follow-up imaging and are associated with persistent neurological deficits such as motor impairment, seizures, or cognitive dysfunction. The identification of such irreversible changes is critical for prognostication and early referral to rehabilitation services. It also emphasizes the role of aggressive management of systemic inflammation and coagulopathy in preventing progression to permanent injury [55].

Diffusion Restriction as a Prognostic Marker

Diffusion-weighted imaging provides one of the strongest prognostic indicators in MIS-C. Restricted diffusion, particularly when associated with ischemic lesions, strongly correlates with poor neurological outcomes. In contrast, lesions without diffusion restriction, such as those seen in PRES or vasogenic edema, typically demonstrate favorable resolution. Incorporating DWI into standardized imaging protocols is therefore essential for risk stratification and management decisions [56].

Longitudinal Imaging and Outcomes

Follow-up neuroimaging studies reveal two broad trajectories. Many children show resolution of white matter and inflammatory lesions within 3–6 months, correlating with full or near-full neurological recovery. However, a subset of patients demonstrate persistent structural changes, including cerebral atrophy or encephalomalacia, which correspond with ongoing functional impairment. These findings highlight the necessity of scheduled follow-up imaging in children with moderate to severe neurological involvement, as radiological persistence often parallels clinical sequelae [57].

Clinical Correlation and Multidisciplinary Implications

Neuroimaging findings must always be interpreted in conjunction with clinical status and laboratory data. Elevated inflammatory markers, thrombocytopenia, and coagulation abnormalities have been shown to correlate with the severity of imaging abnormalities, reinforcing the role of radiology as part of a multidisciplinary approach. Early identification of poor prognostic indicators enables proactive planning for long-term care, including neurocognitive evaluation and rehabilitative therapy. From a systems perspective, integrating radiological prognostication into clinical pathways ensures timely referral and reduces the risk of unrecognized chronic neurological disability [58].

Long-term Sequelae and Follow-up Imaging

Long-term outcomes of MIS-C with neurological involvement vary widely, depending on the extent and type of initial injury. Many children demonstrate complete or near-complete resolution of neuroimaging abnormalities such as white matter hyperintensities, reversible splenial lesions, and PRES within weeks to months. These radiological improvements typically parallel favorable clinical recovery, supporting the role of transient inflammatory injury in the majority of cases [59].

However, a subset of patients develop persistent abnormalities including encephalomalacia, myelomalacia, or cerebral atrophy. These changes are usually associated with severe presentations such as ischemic stroke, hemorrhage, or necrotizing encephalopathy and correlate with chronic neurological deficits such as seizures, motor dysfunction, or cognitive decline [60].

Follow-up MRI is therefore recommended in children with moderate to severe neurological involvement, ideally within three to six months after acute illness. Standardized protocols incorporating FLAIR, DWI, and SWI sequences provide the most prognostic value. Early detection of permanent injury allows for timely initiation

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of neurorehabilitation, educational support, and multidisciplinary follow-up to optimize long-term outcomes [61].

Differential Diagnosis in Pediatric Neuroimaging During COVID-19

The neuroimaging features of MIS-C often overlap with other pediatric inflammatory, infectious, and vascular conditions. Differentiating MIS-C from these entities is crucial, as management strategies and prognoses vary significantly. Radiologists play an essential role in guiding clinicians toward the correct diagnosis by integrating imaging findings with systemic features, laboratory markers, and epidemiological context [62].

Viral Encephalitis

Primary viral encephalitis may present with cortical and subcortical signal abnormalities, sometimes involving the temporal lobes or thalami. Unlike MIS-C, viral encephalitis is more likely to demonstrate cerebrospinal fluid pleocytosis and positive PCR testing for viral pathogens. MIS-C-related encephalopathy often lacks detectable viral RNA in CSF and shows reversible splenial lesions or ADEM-like white matter changes, which favor an immune-mediated process rather than direct viral infection [63].

Acute Disseminated Encephalomyelitis (ADEM)

ADEM shares imaging overlap with MIS-C, presenting as multifocal white and gray matter lesions with variable enhancement. However, ADEM typically follows other viral infections or vaccinations and may occur in the absence of systemic inflammatory or cardiac findings. MIS-C-related ADEM-like lesions usually appear in the context of systemic hyperinflammation, elevated inflammatory markers, and multisystem involvement, which distinguish them clinically and radiologically [64].

Kawasaki Disease with Neurological Involvement

Kawasaki disease (KD) occasionally produces neurological symptoms such as irritability, seizures, or stroke, and neuroimaging may reveal ischemic lesions or cerebral vasculitis. MIS-C and KD share overlapping clinical features, but MIS-C patients are generally older, with more frequent gastrointestinal and neurological involvement, and distinct imaging features such as cytotoxic splenial lesions or PRES. The presence of myocardial dysfunction and elevated D-dimers in MIS-C further helps separate the two conditions [65].

Other Pediatric Inflammatory and Autoimmune Conditions

Conditions such as macrophage activation syndrome, systemic lupus erythematosus, and autoimmune encephalitis can mimic MIS-C both clinically and radiologically. Autoimmune encephalitis may present with cortical or limbic involvement on MRI and associated autoantibodies, whereas MIS-C demonstrates more diffuse, immune-mediated white matter or vascular changes. Careful correlation with serology, inflammatory markers, and exposure history is therefore essential in narrowing the differential [66].

Vascular and Metabolic Disorders

Cerebral venous sinus thrombosis, arterial ischemic stroke, and metabolic encephalopathies may present with imaging abnormalities resembling those in MIS-C. However, the combination of systemic inflammation, recent SARS-CoV-2 exposure, and the characteristic neuroimaging spectrum (splenial lesions, multifocal WM hyperintensities, PRES) provides strong clues in favor of MIS-C. Excluding these alternative diagnoses is critical before initiating immunomodulatory therapy [67].

Conclusion

Neuroimaging has emerged as a cornerstone in the evaluation of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, providing vital insights into disease mechanisms, diagnosis, and prognosis. While systemic features often guide the initial suspicion of MIS-C, the neurological manifestations and their corresponding imaging abnormalities carry significant clinical implications, influencing both acute management and long-term outcomes.

Magnetic resonance imaging, with its superior sensitivity, remains the modality of choice, revealing a spectrum of findings ranging from reversible splenial lesions and ADEM-like demyelination to ischemic infarctions, hemorrhage, and posterior reversible encephalopathy syndrome. Importantly, certain imaging features, particularly diffusion restriction and hemorrhagic lesions, serve as prognostic indicators of adverse neurological outcomes, while reversible changes frequently correlate with recovery. These distinctions underscore the importance of detailed radiological assessment in shaping therapeutic strategies and anticipating sequelae.

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The heterogeneity of neuroimaging patterns reflects the complex interplay of hyperinflammation, endothelial injury, coagulopathy, and autoimmune responses in MIS-C pathophysiology. This emphasizes the necessity of a multidisciplinary approach, where radiology works alongside neurology, pediatrics, and intensive care to optimize patient outcomes. Longitudinal imaging plays a crucial role in documenting lesion evolution, identifying persistent structural changes, and guiding neurorehabilitation strategies for affected children.

As knowledge of MIS-C continues to expand, radiologists are uniquely positioned to contribute not only to individual patient care but also to broader research efforts aimed at refining diagnostic criteria, harmonizing imaging protocols, and clarifying the natural history of post-COVID neuroinflammatory syndromes. Early recognition of characteristic imaging patterns, integrated with clinical and laboratory data, is essential to improve outcomes and reduce the burden of long-term neurological disability in pediatric populations.

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