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Elevated risk for psychiatric outcomes in pediatric patients with Multisystem Inflammatory Syndrome (MIS-C): A review of neuroinflammatory and psychosocial stressors

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ABSTRACT

Multisystem Inflammatory Syndrome in Children (MIS-C) is a secondary immune manifestation of COVID-19 involving multiple organ systems in the body, resulting in fever, skin rash, abdominal pain, nausea, shock, and cardiac dysfunction that often lead to hospitalization. Although many of these symptoms resolve following anti-inflammatory treatment, the long-term neurological and psychiatric sequelae of MIS-C are unknown. In this review, we will summarize two domains of the MIS-C disease course, 1) Neuroinflammation in the MIS-C brain and 2) Psychosocial disruptions resulting from stress and hospitalization. In both domains, we present existing clinical findings and hypothesize potential connections to psychiatric outcomes. This is the first review to conceptualize a holistic framework of psychiatric risk in MIS-C patients that includes neuroinflammatory and psychosocial risk factors. As cases of severe COVID-19 and MIS-C subside, it is important for clinicians to monitor outcomes in this vulnerable patient population.

1. Introduction

Although pediatric presentations of COVID-19 are generally mild, severe and widespread inflammation occurs in patients with Multisystem Inflammatory Syndrome in Children (MIS-C), a secondary inflammatory reaction following infection with the SARS-CoV-2 virus. The Centers for Disease Control and Prevention (CDC) characterizes MIS-C using a six-part definition that includes pediatric age (0–21 years), persistent fever past three days, laboratory evidence of inflammation, signs of organ dysfunction (occurring in cardiac, renal, respiratory, gastrointestinal, dermatologic, and neurological systems), exclusion of an alternative diagnosis, and a close temporal onset with SARS-CoV-2 infection (Figs. 1 and 2). The symptom profile of MIS-C is similar to that of Kawasaki Disease and Toxic Shock Syndrome, but has been found to differ in immunological patterns and certain clinical features (Whittaker et al., 2020). Generally, non-neurological symptoms of MIS-C resolve quickly; most cardiac parameters (Erol and Sari, 2021; Ramcharan et al., 2020; Kapoor et al., 2022) and inflammatory markers (Patnaik et al., 2021) normalize soon after the acute phase of illness. However, long-term neurological and psychiatric symptoms remain inconclusive.

Although there is uncertainty regarding the exact nature of causality between SARS-CoV-2 infection and MIS-C, two pieces of evidence point to a strong argument for causality: 1) Most MIS-C patients test positive for SARS-CoV-2 antibodies (up to 87% in one study (Whittaker et al., 2020)) and 2) There is a strong epidemiological connection between

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COVID-19 and MIS-C infections in regards to timing, patient demographics, and symptomatic profiles (Sancho-Shimizu et al., 2021). Though diagnoses of MIS-C without evidence of SARS-CoV-2 infection have been reported, researchers have attributed the possibility of premature diagnosing to these cases (Campbell et al., 2021). As it stands, COVID-19 and MIS-C are seen as related conditions, with the SARS-CoV-2 virus being the trigger for their respective symptoms.

Existing neurological evidence in COVID-19 literature may provide a window to understanding and predicting similar manifestations in MIS-C patients. Long-term effects of COVID-19 were observed in the UK Biobank COVID-19 re-imaging study, in which tissue damage and decreases in global brain volume were found 141 days (on average) after COVID-19 diagnosis (Douaud et al., 2022). In particular, hospitalized patients showed greater reductions of gray-matter than non-hospitalized counterparts, suggesting that hospitalization may present a unique risk factor in neurological outcomes. Considering that MIS-C patients face a high risk for hospitalization, the longitudinal findings of this COVID-19 study may inform similar developments in MIS-C populations. Furthermore, MIS-C presents unique challenges on the basis of disease experience. Compared to the symptomatology of COVID-19 in children, MIS-C is more critical and results in a higher hospitalization period of eight days (Hoste et al., 2021). Therefore, the elevated severity of the disease and hospitalization experience of MIS-C patients may result in more expansive psychiatric and neurological outcomes.

This is the first review to summarize potential connections between neuroinflammation, psychosocial disruptions, and psychiatric risk in MIS-C patients The purpose is to cover two domains of evidence that project long-term psychiatric outcomes for children with MIS-C. Beginning with the neurophysiological effects of MIS-C, we dissect potential associations between neuroinflammation and psychiatric risk through immune-mediated mechanisms. Next, we discuss MIS-C as a deleterious psychosocial experience, characterized by pandemic-related stressors, long periods of hospitalization, and social isolation that may disrupt early cognitive development. Together, the neurophysiological and psychosocial disruptions involved in the disease progression of MIS-C may confer deleterious psychiatric outcomes during both the short-term and long-term post-illness phases.

2. Search strategy and selection criteria

Sources were generated for this narrative review through a search of PubMed and Google Scholar using "MIS-C″ and "Paediatric Inflammatory Multisystem Syndrome (PIMS)" to define the syndrome, since the two terms are interchangeable in many articles. After filtering papers by publication dates, between January 2020 and August 2023, we added an additional filter for articles published in English. More specific studies regarding subtopics of neuroinflammation and psychosocial disruptions were identified using keywords such as "psychiatric", "neurologic", and "neuropsychiatric", which were used to find papers relating to neuropsychiatric outcomes (92 papers). To analyze the effects of the pandemic on psychosocial stress, the keywords "COVID-19" and "psychocological" were used to generate 1896 results, which were then rerun with additional keywords of "MIS-C," "social isolation", "school closures", "abuse," "food insecurity," "hospitalization," "caregiver loss," and "early life adversity" in order to generate articles of a more specific topical interest. All studies, including meta-analyses, reviews, cohort, case-control, and case-report studies were included as eligible references, although they were not included if full-text was unavailable. Reference lists were also scanned to find additional relevant papers, and no additional information was sought by contacting authors, publishers, etc. A total of 280 papers were read and analyzed, and 112 were included as references in this paper; 65 papers were drawn from our search process, while an additional 47 papers were referenced for contextual support. Guidelines for the PRISMA-S checklist (Rethlefsen et al., 2021) were followed as they pertained to the scope of the paper. Figures were generated using Biorender and hand-drawn illustrations.

3. Summary of psychiatric findings in MIS-C (Table 1)

In MIS-C patients, acute onset psychosis and hyperactive delirium have been cited in multiple case studies and small cohorts (Hutchison et al., 2020; Ngo et al., 2021) (Table 1), and researchers have found general increases in social interaction, mood, and behavioral difficulties (Sa et al., 2021; Penner et al., 2021; Enner et al., 2022; Abbati et al., 2022). In a six-month follow-up study of a cohort in the United Kingdom, researchers cited "severe emotional difficulties" in 22% of the MIS-C cohort (self-report) and neurological impairment in 39% of patients at the point of the six-month follow-up (Penner et al., 2021). Another study by Enner and colleagues outlined a more detailed profile of psychiatric, neurological, and sleep symptoms in MIS-C patients at both admission and a 23-week follow-up. In this study, psychiatric assessments in MIS-C patients noted significant mood and personality change, excessive daytime sleepiness, nocturnal arousals, and difficulties falling asleep. Furthermore, the authors found that symptoms across all three domains persisted through the 23-week follow-up in over half of their MIS-C cohort, which underscores the unique long-term nature of these neuropsychiatric symptoms (Enner et al., 2022). Strikingly, there is also a clear differentiation in neuropsychiatric findings between pediatric COVID-19 and MIS-C patients: Abbati and colleagues found that neurological signs and symptoms were present in 66% of their MIS-C cohort, compared to 31% of their COVID-19 cohort (Abbati et al., 2022). More research is needed to understand how psychiatric symptoms develop in this at-risk patient group and how they may differ between MIS-C and COVID-19. Currently, no validated survey currently exists for analyzing these symptoms in MIS-C patients, so future studies will be valuable in outlining parameters for MIS-C psychiatric assessment tools.

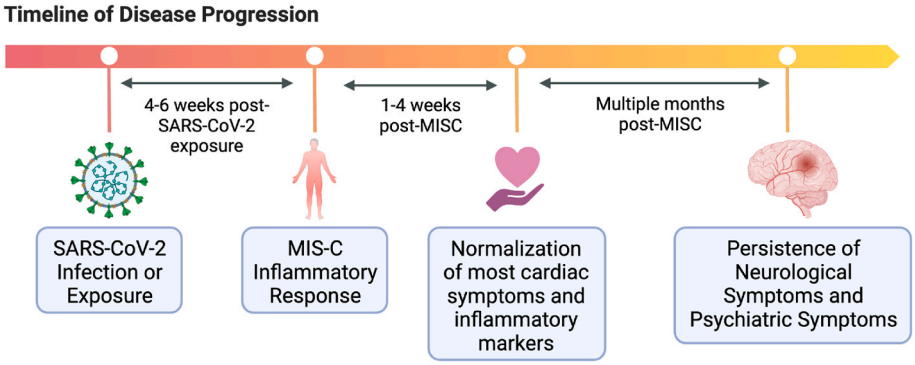

Fig. 1. An overview of the MIS-C disease course.

4. Domain 1: findings of neuroinflammation in MIS-C (Fig. 3)

The prevalence of neurological symptoms have been described ranging from 22 to 88% of MIS-C cohorts (Ray et al., 2021; LaRovere et al., 2021; Mihai et al., 2022)– a wide range that may be attributed to a lack of standardized symptom definitions. Generally, higher rates of neurological symptoms are observed in MIS-C patients in comparison to COVID-19 patients. Neurological MIS-C studies have found varied imaging findings, such as acute disseminated encephalomyelitis (ADEM), acute necrotizing encephalopathy (ANE), lesions of the corpus callosum, peripheral nervous system involvement, ischemic stroke, myelitis, and myositis (Abdel-Mannan et al., 2020; Palabiyik et al., 2021; Ray et al., 2021). The most common findings and their implications for psychiatric risk are discussed below (Fig. 3).

5. Neurological finding: general encephalopathy in MIS-C

A broad profile of encephalopathy has been described in MIS-C, including seizures, headaches, dysarthria, dysphagia, cerebellar ataxia, hallucinations, neck stiffness, drowsiness, irritability, confusion, and inability to walk (Sa et al., 2021; Enner et al., 2022; Ray et al., 2021; Palabiyik et al., 2021; Zubair et al., 2020; Abel et al., 2020). Headaches are one of the most common neurological symptoms in MIS-C patients, potentially caused by the activation of nociceptors by upregulated inflammatory markers. Considering the areas of inflammation seen in MIS-C patients, such as the hypothalamus (a regulator of sleep, hormone control, and homeostasis (Saper and Lowell, 2014)) and cerebellum (coordination and motor control), it is possible that neuroinflammation may exacerbate sleepiness and cerebellar ataxia (Fig. 3A). In regards to sleep disturbances, sleep symptoms and excessive daytime sleepiness have been found in up to 85% of MIS-C patients (Enner et al., 2022), with 37% of patients continuing to experience symptoms after a 23-week follow-up. Previous research has proposed a link between excessive daytime sleepiness and depression (Liu et al., 2018), therefore making it important for more studies to investigate the onset and persistence of sleep symptoms in MIS-C patients as they potentially relate to psychiatric risk.

6. Neurological finding: acute disseminated encephalomyelitis (ADEM) in MIS-C (Fig. 3B)

Acute disseminated encephalomyelitis (ADEM) is a monophasic disease that causes demyelination in the CNS and is often preceded by viral infection (an etiological parallel to how MIS-C is preceded by SARS-CoV-2 infection). In a radiological imaging study of 45 MIS-C patients by Palabiyik and colleagues, ADEM lesions were found in the cerebellar hemispheres, periaqueductal region, bilateral hypothalamic region, bilateral thalamus, lentiform nucleus, caudate nucleus, and deep white matter and subcortical area of one patients (Palabiyik et al., 2021). These manifestations disappeared after five days, but new pathophysiological changes, such as posterior reversible encephalopathy (PRES), were observed in the parietooccipital and frontoparietal regions (Fig. 3C). In another study of MIS-C patients, ADEM was present in six MIS-C patients and was localized to the bilateral frontal lobes, thalami, and basal ganglia (LaRovere et al., 2021). The prognosis for ADEM patients is generally positive, with most symptoms resolving after a couple of weeks. However, some studies have cited persistent cognitive and social impairments following ADEM in childhood, suggesting that even monophasic illnesses in the CNS can lead to long-term consequences on behavior and cognition (Otallah, 2021; Jacobs et al., 2004).

7. Neurological finding: splenial lesions of the corpus callosum in MIS-C (Fig. 3D)

Splenial lesions in the corpus callosum are common MRI findings in MIS-C patients with neurological manifestations (Ray et al., 2021; Abdel-Mannan et al., 2020; Lindan et al., 2021). Reversible splenial lesion syndrome (RESLES) is a temporary lesion of the corpus callosum that often co-occurs with other forms of encephalopathy and is preceded by viral infections (Bektaş et al., 2021). In three other neurological studies of MIS-C, lesions in the corpus callosum were found in 40–100% of patients (Abdel-Mannan et al., 2020; Lindan et al., 2021; Ray et al., 2021). Because the corpus callosum continues to mature through late childhood and adolescence (McGuire, 2016), lesions due to MIS-C may disrupt maturation of this key white matter tract. Multiple studies have found associations between reductions of integrity in the corpus callosum with numerous psychiatric illnesses (Benedetti et al., 2011; Han et al., 2014), and some researchers have noted specific impairments in the splenium of patients with depression (Cole et al., 2012). Because the corpus callosum holds important projections to the cortex, it is possible that lesions (even temporary ones) may cause long-term disruptions to interhemispheric communication and cortical functioning.

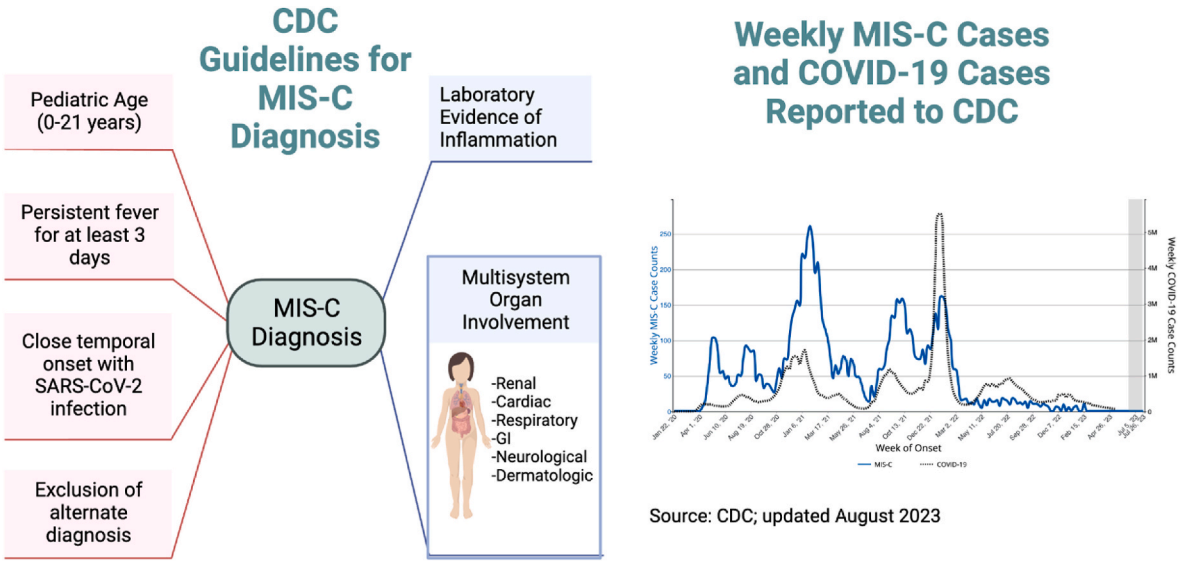

Fig. 2. The components of an MIS-C diagnosis, with the number of cases of MIS-C (blue) over the course of the pandemic, compared to the number of COVID-19 cases (dashed). As of August 2023, there have been 9518 cases of MIS-C reported in the United States.

Table 1
Summary of studies finding psychiatric outcomes in MIS-C patients.

Authors (Year)	Cohort/Methods	Findings
Rollins et al. (2023) (Rollins et al., 2023)	64 children with MIS-C were assessed on working memory, executive functioning, behavioral symptoms, and quality of life 6–12 months following hospital discharge (mean age = 11.5 years).	MIS-C patients exhibited greater neurological abnormalities and behavioral symptoms, worse working memory, and lower quality of life
Otten et al. (2023)	69 children with MIS-C, 49 of these were assessed during a 4-month follow-up after PICU discharge (median age = 11.6 years).	In 29 children that underwent extensive training, there were relatively worse performances in visual memory, attention, and planning, lower quality-of-life scores, increased fatigue, and an increased risk for PTSD in 33.3% of MIS-C patients.
Abbati et al. (2022)	95 children in COVID-19 group (median age = 0.94 years) and 27 children in MIS-C group (median age = 8.5 years) were assessed for neurological symptoms.	In comparing the COVID-19 and MIS-C groups, MIS-C patients more often had multiple neurological involvements and the following symptoms: consciousness reduction until stupor, confusion, mood and behavioral disorders, meningism, dysgeusia, and speech impairment.
Enner et al. (2022)	47 patients diagnosed with MIS-C (median age = 10 years) and a control group of patients with an ICU stay (median age = 10 years) were assessed prior, during, and 23 weeks after hospitalization for neuropsychiatric symptoms.	Neuropsychiatric symptoms were elevated in MIS-C patients. At the time of hospitalization, the following symptoms were reported: neurological (85%), sleep (85%), psychiatric (59%), and mood/behavioral (52%). At follow-up, these symptoms were persistent: neurological (37%), sleep (37%), psychiatric (44%), and mood/behavioral (40.5%).
Penner et al. (2021)	46 children with Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) (median age = 10.2 years) were followed up 6 weeks and 6 months after hospitalization. The PedsQL was administered at 6 months.	Family trauma and anxiety were commonly reported in this cohort. Severe emotional difficulties were reported at 6 months in 18% of parent reports and 22% of self reports.
Ngo et al. (2021)	5 pediatric COVID-19 patients (age range = 1.4–15 years) with neuropsychiatric symptoms were recruited, and 4 of these patients had MIS-C. Cytokine, chemokine, and SARS-CoV-2 antibody profiles were also characterized using cerebrospinal fluid (CSF).	Out of the 4 MIS-C patients, 3 had acute onset psychosis, while another had seizures and encephalopathy. Additionally, CSF analysis showed a positive correlation between SARS-CoV-2 antibodies and pro-inflammatory cytokines and chemokines. MIG, MPC, MIP-1β, and TARC were elevated in their COVID-19 cohort.
Hutchison et al. (2020)	Case study of a single 14-year-old boy	Authors reported fluctuating impairments in awareness and attention, psychosis, and agitation that were typical of acute hyperactive delirium.
Bentes et al. (2023)	Single-center prospective study of 3021 pediatric patients admitted to a hospital for infectious disease	232 patients were found to have COVID-19, and 21 of these patients (9%) showed neurological manifestations. 14/21 of these patients developed MIS-C.

8. Neurological finding: peripheral nervous system involvement (Fig. 3F)

Peripheral nervous system involvement is commonly found in MIS-C patients and may present as Guillain Barré Syndrome (GBS), a monophasic disease of the peripheral nerves and roots caused by previous infection, manifesting as muscle weakness and paralysis (Shahrizaila et al., 2021). In three studies, peripheral nervous system involvement was found in MIS-C patients (Abdel-Mannan et al., 2020; LaRovere, 2021), although not all were described as GBS. The pain and loss of functionality resulting from peripheral nerve injury can lead to psychiatric outcomes– in a review of GBS patients, GBS was found to cause profound psychiatric disturbances, including stress, anxiety, depression, fatigue, sleep abnormalities, visual hallucinations, paranoid delusions, disorientation, terror, and psychosis (Hillyar and Nibber). In MIS-C patients, the confluence of GBS with other severe forms of inflammation that impact daily functioning may cumulatively compound risk for psychiatric disorders.

9. The unclear pathogenesis of neurological manifestations in MIS-C

The neurological manifestations listed above are consistent findings within the MIS-C literature, but a thorough understanding of the pathogenesis of these manifestations is lacking. The cause of inflammation, although inconclusive, does not seem to involve direct binding and replication of the SARS-CoV-2 virus in brain tissue. While there has been evidence of SARS-CoV-2 antibodies in the cerebrospinal fluid (CSF) of patients with COVID-19, there is no such evidence that exists in MIS-C literature (Abdel-Mannanet et al., 2020; Bentes et al., 2023). Instead, researchers have attributed the possible causes of inflammation to cytokine storm syndrome, dysregulated immune responses after SARS-CoV-2 exposure, vascular dysfunction, and autoimmune mechanisms. It is possible that these mechanisms co-occur in a biphasic model, in which an early disruption to immune functioning leads to increased vascular permeability (especially in the blood-brain-barrier) and further insults of harmful chemokines/cytokines to the brain (Xu et al., 2022; Yang et al., 2021; Spudich and Nath, 2022). Even mild respiratory infection can lead to robust neurological damage, such as myelin loss, decreased oligodendrocytes, and impaired hippocampal neurogenesis (Fernández-Castañeda et al., 2022). This evidence suggests that many of the neuroinflammatory manifestations seen in MIS-C patients may actually be driven by systemic inflammation, rather than direct invasion of the SARS-CoV-2 virus into the central nervous system.

Within the brain, analyses of CSF have reported cases of non-specific pleocytosis (increased cell count) and cytokine upregulation (Ngo et al., 2021; Chen, 2020; Kest et al., 2020), suggestive of meningitis, brain inflammation, and immune dysregulation. Outside of the brain, systemic cytokine signatures can also be incredibly informative. Gurlevik and colleagues profiled biomarkers and cytokines in blood samples from MIS-C and COVID-19 patients (Gurlevik et al., 2022). In addition to recapitulating evidence of elevated white blood cell count, CRP, PNL, Procalcitonin, BNP, and CK-NB found in other studies, they also found that IL-17A, IL-18, and MIG/CXCL9 were uniquely elevated and could potentially contribute to the specific pathogenesis of MIS-C inflammation. Paralleling these findings are additional studies that have uncovered a unique profile of immune dysregulation in MIS-C patients including IL-18, IL-6, IL-27, M-CSF, CXCL5, CXCL11, CXCL1, and CXCL6, with some recapitulating the increases of CXCL9 and IL-17A that differentiate patients with MIS-C from those with severe COVID-19 (Rodriguez-Smith et al., 2021; Diorio et al., 2021; Consiglio et al., 2020; Gruber et al., 2020; Carter et al., 2020; Huang et al., 2022). The origin of these markers may be 1) the trafficking of peripheral cytokines, immune cells, and antibodies to the brain parenchyma following systemic endothelial activation, and/or 2) byproducts of brain inflammation. From this broad array of findings in MIS-C patients, we not only can

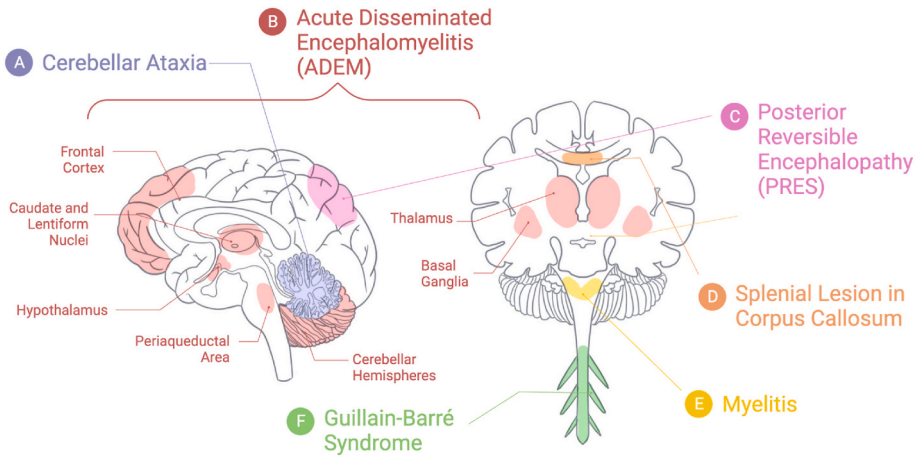

Fig. 3. Neurological manifestations and associated brain areas found in MIS-C studies. We summarize the discussed manifestations of neurological conditions in MIS-C patients, including cerebellar ataxia (Fig. 3A), acute disseminated encephalomyelitis in frontal cortex, hypothalamus, periaqueductal area, caudate and lentiform nucleus, cerebellar hemispheres, thalamus, and basal ganglia (Fig. 3B), posterior reversible encephalopathy (PRES) in the parietooccipital cortex (Fig. 3C), splenial lesions of the corpus callosum (Fig. 3D), myelitis in the spinal cord (Fig. 3E), and Guillain-Barré syndrome and peripheral nervous system involvement (Fig. 3F).

formulate a general understanding of MIS-C as a global inflammatory event in the body and brain, but also look at recurring biomarkers IL-17A and CXCL9 as more specific links between inflammation and psychopathology.

10. Expanding on the link between neuroinflammation and psychopathology

There is no proven pathway between neuroinflammation and psychopathology. However, with existing evidence that IL-17A and CXCL9 are uniquely elevated in MIS-C, we present a hypothetical framework to connect these specific inflammatory markers to processes of neurotransmitter metabolism that may contribute to psychiatric pathologies. Broadly speaking, neuroinflammation has widespread effects on cytokine production in the brain, glutamate metabolism, microglial/astrocytic activation, oxidative stress, and epithelial functioning (Najjar et al., 2013; Reus et al., 2015). The disruption of one aspect of this functioning can cause a positive feedback system that further dysregulates the other components. Within the brain, inflammatory markers may contribute to microglial activation, which then potentiates widespread effects on neuronal integrity, synaptic plasticity, and glutamatergic and serotonergic transmission (Najjar et al., 2013; Kreisel et al., 2014). The upregulation of cytokines may also alter the activity of tryptophan-degrading enzymes and decrease overall levels of tryptophan and serotonin, which have been correlated with increased depression scores (Dantzer et al., 2011).

11. Hypothesis: connecting CXCL9 to psychopathology

This process can be more specifically linked to MIS-C in the example of CXCL9, which has been noted by many studies as being uniquely elevated in both MIS-C and COVID-19 patients (Gurlevik et al., 2022; Rodriguez-Smith et al., 2021; Diorio et al., 2021; Huang et al., 2022; Caldarale et al., 2021). CXCL9, also known as chemokine (C-X-C motif) ligand 9, is a chemokine that regulates T cell migration during immune responses, notable for its chemoattractant nature for Th-1 (pro-inflammatory) cells (Coperchini et al., 2021). It modulates the release of interferon-gamma (IFN-γ), which can further potentiate release of CXCL9 in a positive feedback loop that activates the harmful microglial phenotype. In a COVID-19 study of patients experiencing neurological symptoms, an analysis of CSF found marked increases of IFN-γ and CXCL9 nearly 2 months after SARS-CoV-2 infection (Remsik et al., 2021), suggesting a long-term increase of these inflammatory markers that may be connected to neurological sequelae. These increases of Th-1 pro-inflammatory cytokines may also potentiate the activation of enzymes that produce quinolinic acid, an N-methyl-D-aspartate receptor (NMDAR) agonist that may lead to hyperglutamatergia (Najjar et al., 2013).

Hyperglutamatergia can be associated with certain neurological manifestations. Glutamate, which is an excitatory neurotransmitter, binds onto N-methyl-D-aspartate receptors (NMDARs) to execute important brain functions relating to signaling and synaptic plasticity, and a healthy balance of glutamate is essential for normative brain functioning (Lener et al., 2017). Lindan and colleagues found anti-N-methyl-D-aspartate-receptor (anti-NMDAR) antibodies in an COVID-19 patient who developed anti-NMDAR autoimmune encephalitis (Lindan et al., 2021), in which the binding of IgG antibodies to the NR1 subunit of NMDARs causes an internalization of NMDARs from the synapse that can last for multiple hours (Kayser and Dalmau, 2016). As a result, the sustained lack of NMDARs may prevent glutamate from being taken from extracellular space, ultimately contributing to a sustained excess of glutamate in the synapse (Manto et al., 2010). Additionally, hyperglutamatergia can help to explain the development of splenial lesions of the corpus callosum: glutamate may supplement the excitotoxic action of NMDARs, which in tandem with sodium-potassium channels, contribute to water flow into astrocytes and neurons in the corpus callosum and manifest in the hyperintensity seen in many MIS-C brain images (Blaauw and Meiners, 2020; Sahu et al., 2021). This dysregulation in NMDARs has psychiatric implications: in a meta-analysis by Pearlman and colleagues, individuals with schizophrenia, schizoaffective, bipolar, or major depressive disorders were three times more likely than healthy controls to have elevated NMDAR antibody titers (Pearlman and Najjar, 2014).

12. Hypothesis: connecting IL-17A to psychopathology

Additionally, elevations of systemic IL-17A (another cytokine profiled in MIS-C studies) have been associated with numerous processes that disrupt neuronal signaling and Blood-Brain-Barrier (BBB) function (Cao et al., 2021). In a rodent study that researched the effects of IL-17A, IL-17A injection was associated with increased depressive-like behavior, elevations of inflammatory cytokines (IL-6 and TNF-α) in the hippocampus, and increased NF-κB and p38/MAPK signaling in the hippocampus and prefrontal cortex (Nadeem et al., 2017). Later, inhibition of these signaling pathways normalized behavior and cytokine levels, suggesting the IL-17A is directly involved in the activation of pro-inflammatory cytokines and signaling pathways associated with depressive-like behavior. Another recent study presents evidence for

IL-17A as a biomarker of antidepressive treatment resistance, noting that the level of IL-17A rose significantly in the non-responder group compared to the responder during treatment for Major Depressive Disorder (MDD) (Nothdurfter et al., 2021). In the context of the growing evidence linking IL-17A to MDD, it is more pertinent to consider how the unique elevation of IL-17A in MIS-C patients may contribute to greater risk for future psychopathology.

The pathways connecting neuroinflammation with psychopathology are not well studied– and yet, evidence exists for connecting MIS-C-specific biomarkers with known mechanisms of psychopathology. In particular, we have linked studies that have profiled CXCL9 and IL-17A as unique biomarkers of MIS-C with those showing how these biomarkers may lead to disrupted neurotransmitter metabolism and cytotoxic potentiation in the brain. In addition to this neuroimmunological explanation, we also discuss the psychosocial implications of the MIS-C disease experience in the following section.

13. Domain 2: MIS-C as a psychosocial stressor

MIS-C is a disease experience that uniquely presents early life adversity (ELA) during a critical window of childhood brain development. ELA is a multi-faceted experience that encompasses social, economic, and familial domains, resulting in significant disruptions to neural development and behavior (Smith and Pollak, 2020). In fact, adults with multiple adverse childhood experiences (ACEs) are at considerably higher risk for substance abuse and mental illness (Hughes et al., 2017). In the pathophysiology of such outcomes, ELA disrupts the development and function of the hypothalamic-pituitary-adrenal (HPA) axis, the main regulator of the stress hormone cortisol. ELA, particularly maltreatment, is associated with HPA-axis hyperactivity and an upregulation of cortisol production, followed later by periods of hypocortisol in early adulthood. The key component of ELA is timing; adverse events during childhood result in greater variability in the methylation of brain-derived neurotrophic factor (BDNF) (Dunn et al., 2019; Roth et al., 2009), more pronounced fluctuations in HPA-axis activation (Albers et al., 2008), further release of glucocorticoids, and greater disruptions to hippocampal neurogenesis (Lajud and Torner, 2015) during early critical periods in brain plasticity. These neurobiological processes, as they are dysregulated in the MIS-C disease experience, may play an important role in the pathogenesis of psychiatric outcomes.

Furthermore, ELA has been shown to potentially increase a wide range of inflammatory markers that are similarly upregulated in MIS-C, such as IL-6 (Lacey et al., 2020), TNF-α, and CRP (Iob et al., 2022; Baumeister et al., 2016). A recent meta-analysis by Kulhman and colleagues also found an association between adversity and serum levels of CRP (but not IL-6) when analyzing multiple studies (Kuhlman et al., 2020). The effect size of this finding was small, which the authors attributed to the masking effect of glucocorticoids that are released following adversity and stress. This masking effect is diminished in adolescence when cells become more glucocorticoid-resistant, which potentially projects a greater inflammatory response for adolescents compared to infants/young children. This time-dependent effect is important to consider in the context of MIS-C, since ELA-induced inflammation may only appear multiple years following the acute phase of illness.

14. Psychosocial impact of pandemic-related stressors

Adverse childhood experiences (ACEs)– specifically food insecurity (Huizar et al., 2021), loss of primary caregivers (Hillis et al., 2021), incidences of domestic violence (Piquero et al., 2021), substance use (Schmidt et al., 2021a), social isolation (Kılınç et al., 2021), and child abuse (Sserwanja et al., 2021; Rengasamy et al., 2021), have increased over the course of the COVID-19 pandemic. And with pandemic-related quarantines and school closures, there were additional disruptions to school resources such as psychological services, counseling, food distribution, and physical fitness classes that are essential for healthy childhood development (Rajabi, 2020; Hoffman and Miller, 2020). For children who rely on stable settings of care and enrichment to thrive, these disruptions contributed to a considerable amount of uncertainty and stress. So far, studies have found substantial emotional disturbances and psychiatric symptoms in children during the pandemic. One study on the effects of COVID-19 on pre-adolescent children outlined wide-scale increases in emotional symptoms, hyperactivity, and conduct problems among school-aged children (Waite et al., 2021). In younger children, two studies reported higher levels of fear, clinginess, externalizing problems, and oppositional-defiant behaviors (Nearchou et al., 2020; Schmidt et al., 2021b). In more vulnerable pediatric groups with Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD), the loss of daily routines and special needs services at school may have also contributed to distress and psychiatric symptoms (Jefsen et al., 2021). As seen in these studies of the pandemic to date, the aggregation of adverse childhood experiences may contribute to greater rates of pediatric psychological distress.

MIS-C children may also be at risk of experiencing greater levels of environmental stressors due to socioeconomic disparities in MIS-C risk and prevalence (Dennis-Heyward, 2021). In a recent study that studied the association between MIS-C and Child Opportunity Index (COI: a measure of the environmental resources important for healthy childhood development) (Acevedo-Garcia et al., 2020), children who scored lower in overall COI had significantly higher odds of being diagnosed with MIS-C compared with children who scored higher (Tyris et al., 2022). Therefore, this indicates that a substantial number of MIS-C patients may also live in neighborhoods with lower health, educational, and nutritional resources, which are markers of childhood adversity that may further increase stress and psychiatric risk (Jackson and Beaver, 2015; Lowe et al., 2016).

15. Psychosocial impact of MIS-C hospitalization

In addition to COVID-19 pandemic-related childhood stress, the MIS-C disease experience often leads to hospitalization and critical care support (Radia et al., 2021; Dufort et al., 2020), potentially presenting as a second-hit stressor to the disease itself. Hospitalization often requires leaving friends and family for several days and entering an unpredictable medical setting with pain, examinations, and uncertain health outcomes. Hospitalized children face higher rates of anxiety (Delvecchio et al., 2019), and PICU admission is also associated with short- and long-term psychiatric morbidity. 10–30% of children who require PICU admission also develop short-term Post-Traumatic Stress Disorder (PTSD), and many cognitive, emotional, and behavioral difficulties can extend 10–15 years post-admission (Ko et al., 2022). Among COVID-19 patients, the prevalence of psychiatric manifestations is four times higher in hospitalized children compared to adults (Ray et al., 2021), underscoring a distinct vulnerability for psychiatric disorders in children. At a young age, children may lack the ability to adjust and cope in stressful medical situations, consequently facing greater risk for psychopathology in the aftermath of MIS-C hospitalization.

MIS-C hospitalization is a stressful experience for parents, caretakers, and family members that may disrupt care in a multitude of ways. The only study to directly evaluate caretaker stress levels in response to MIS-C hospitalization took place in Greece, where authors found measures of higher stress levels in parents and children hospitalized for either COVID-19 or MIS-C, compared to cases in which children were not hospitalized for COVID-19 (Gkentzi et al., 2022). Another study found that among parents of hospitalized children in the PICU, reports of new mental illness nearly doubled (Logan et al., 2020). Loss of child care (due to school and daycare closures), in tandem with financial stress (due to job loss and MIS-C hospitalization fees), can confer considerable stress onto parental responsibilities and contribute to worsening mental health outcomes during the pandemic (Patrick et al., 2020; Cheng et al., 2021). The stress experienced by the parents/family members may

manifest in altered parental behaviors that negatively impact the child (Chung et al., 2020), potentially contributing to attachment and temperament issues in childhood (Stelter and Halberstadt, 2011; McQuillan et al., 2017) and greater risk for long-term emotional problems through adolescence (Bakoula et al., 2009). MIS-C hospitalization, as it relates to a wide variety of stressors in the lives of both patients and caretakers, is important to consider as an additional risk factor for psychiatric disorders in affected children.

The pathway between early life adversity and psychopathology is well-studied and highly integrative (Lahdepuro et al., 2019; Taylor, 2010). In the same way that the neurobiological manifestations of MIS-C inflammation may confer a multitude of disruptions onto brain processing, early life stress has been shown to affect many brain circuits that underlie healthy psychosocial functioning (Teicher et al., 2016; Fareri and Tottenham, 2016; Delpech et al., 2016; Demir-Lira et al., 2016). Stress, particularly during the critical period of early childhood brain plasticity, dysregulates the prefrontal-hypothalamic-amygdala circuit, autonomic nervous system, and dopaminergic reward system (Smith and Pollak, 2020)– which are all essential for hormonal control, executive functioning, coping, emotional processing, memory, and general cognition. In other words, early adverse experiences, such as the hospitalization experience of MIS-C, are stressors that interfere with childhood brain development on a comprehensive scale, thereby raising risk for future psychopathology.

16. Future clinical considerations

As detailed throughout this review, children and young people with MIS-C are at high risk for developing neurological, psychiatric, and developmental complications in the acute and long-term course of their disease experience. Furthermore, it is crucial to consider how the positive feedback system between psychosocial stress and inflammation may have compounding effects on future risk for psychopathology. As MIS-C research currently stands, there are few studies measuring acute or longitudinal effects on psychiatric disturbance. Short-term neurological disturbances in MIS-C and the trauma of severe disease may not just increase psychiatric risk, but also lead to long-term neurodevelopmental effects (Singer et al., 2021). MIS-C will continue to be a risk factor for children across the world, and increased vigilance from clinicians and researchers is needed to effectively treat this psychiatric risk group. Future work should focus on quantifying psychiatric symptoms, emotional disturbances, and stress in MIS-C patients and families during evaluation and subsequent follow-ups. Additionally, racial, social, and economic factors may uniquely contribute to risk and adversity in the MIS-C experience, and these variables should be measured in future studies. More funding should be directed towards quantifying multifaceted risk factors and outcomes in new MIS-C cohorts, in addition to supporting ongoing longitudinal studies of established MIS-C cohorts.

In summary, we gathered evidence from neurological findings and psychosocial components of the MIS-C disease experience, integrating both into a theoretical framework for hypothesizing potential connections to psychiatricc risk. Understanding these factors will be critical for future approaches in analyzing risk, treatment policy, follow-up studies, and long-term care of MIS-C patients.

CRediT authorship contribution statement

Tracy Pan: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Meghan E. Gallo:** Supervision, Writing – review & editing. **Kirsten A. Donald:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Kate Webb:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Kevin G. Bath:** Supervision, Writing – review & editing.

Declaration of competing interest

All authors report no conflict of interest.

Data availability

No data was used for the research described in the article.

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