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Report of a Child With Febrile Status Epilepticus and Post-COVID Multi-System Inflammatory Syndrome

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Abstract

Multi-system Inflammatory Syndrome in Children (MIS-C) is a post infectious inflammatory syndrome following COVID infection. Previous case series have demonstrated that CNS involvement is less common and presents heterogeneously. The following case describes an infant with an initial presentation of refractory febrile status epilepticus. Genetic testing later showed multiple variants of uncertain significance. The patient met clinical criteria for MIS-C and had a markedly abnormal brain MRI with bilateral diffuse restricted diffusion (anterior > posterior). Clinically, the patient improved with pulse steroids and IVIg. This case highlights the importance of maintaining MIS-C in the differential as a trigger of Febrile Infection Related Epilepsy Syndrome (FIRES) with multi-organ involvement presenting 2-4 weeks after infectious symptoms and COVID exposure.

Keywords

COVID, multi-system inflammatory syndrome in children, status epileptics, febrile infection related epilepsy syndrome (FIRES), abnormal brain MRI

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Introduction

Multi-system Inflammatory Syndrome in Children (MIS-C), or Pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (PIMS-TS) is a post COVID-19 inflammatory disorder first described in April 2020 in the United Kingdom. COVID-19 has previously been described as a benign infection in children, but this post-infectious inflammatory syndrome has been shown to more often result in ICU admissions than COVID infection alone.[1,2] Although clinically similar to Kawasaki arteritis, it is a heterogeneous condition with a more variable clinical presentation. Clinical criteria for MIS-C outlined by the CDC include: age less than 21 years old presenting with fever, laboratory evidence of inflammation, multi-organ ($\geq$2) involvement; with no alternative diagnosis; and positive COVID RT-PCR or IgG, or known exposure to COVID-19 within 4 weeks of symptom onset.[3]

The pathobiology for developing MIS-C is poorly understood. It has been observed that African Americans and Latino Americans are at higher risk of developing MIS-C than Caucasians but specific genetic and environmental factors have yet to be identified.[4,5] A case series in the United Kingdom evaluated 50 patients infected with COVID-19 and 27 of them later developed symptoms consistent with MIS-C. Four of these 27 patients had neurologic involvement (both the CNS and PNS) in the absence of respiratory symptoms.[6] The

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following case describes a Mennonite patient initially presenting with febrile status epilepticus, later diagnosed with MIS-C, and found to have 5 genetic variants on an epilepsy panel. This case highlights a unique, severe presentation of MIS-C in a young child with neurologic involvement.

Case Presentation

A previously healthy and developmentally normal 12-month-old male presented with febrile status epilepticus (bilateral tonic-clonic with upward eye deviation) to the emergency department. He required 3 anti-seizure medications i.e. fosphenytoin, levetiracetam, and phenobarbital to control initial seizures and was intubated for airway protection. He was placed on continuous EEG (cEEG) monitoring which showed diffuse high voltage delta slowing of the background and intermittent generalized and multifocal onset electrographic seizures without clinical changes. Seizure frequency was around 3 times per day lasting between 10 minutes to 2 hours. Midazolam drip was added. His last seizure was on day 7. Midazolam drip was discontinued on day 9. The patient had cardiogenic shock suspected to be due to myocardial inflammation requiring 2 vasopressors, which were discontinued by day 6. He has a family history of febrile seizures on both maternal and paternal sides and maternal grandmother has epilepsy. He had preceding mild flu-like symptoms 1 month prior and known COVID exposure.

Table 1. Patient Laboratory Findings.

Labs	Patient's values	Reference range
WBC	2.26 K/μl	6.0-17.5 K/μl
Absolute lymphocyte count	0.48 K/μl	3.0-13.5 K/μl
Hemoglobin	7.4 g/dl	10.5-13.5 g/dl
Platelets	105 K/μl	158-470 K/μl
CRP	5.7 mg/dl	<0.50 mg/dl
Procalcitonin	59.54 ng/ml	<0.08 ng/ml
Ferritin	452.4 ng/ml	30.0-400 ng/ml
PT	17.5 seconds	12.0-14.2 seconds
PTT	47 seconds	23-35 seconds
D-dimer	2.34 μg/ml	<0.54 μg/ml
Troponin	0.045 ng/ml	<0.010 ng/ml
BNP	1,924 pg/ml	<125 pg/ml
LDH	711 unit/L	135-250 unit/L
AST	208 unit/L	0-40 unit/L
ALT	85 unit/L	0-41 unit/L
Albumin	3.1 g/dl	3.5-5.2 g/dl
Creatinine	0.3 mg/dl	0.2-0.4 mg/dl

COVID IgG was positive. Additional labs demonstrated evidence of inflammation, elevated troponin and BNP, anemia, and thrombocytopenia (Table 1). Transthoracic echocardiogram (TTE) showed normal coronary arteries without any depression in ejection fraction. Cerebrospinal fluid was normal. Epilepsy panel showed variants of uncertain significance in SCN1A, PCDH19, RELN, CACNA1 H, and MTOR, which were inherited (Table 2). This was clarified by parental genetic analysis which showed the presence of these variants in either the child's mother or father, who did not have epilepsy.

Additional work-up included urine organic acids, serum amino acids, and ammonia to evaluate for metabolic processes, which were reassuring. Serum anti-NMDA receptor, anti-NMO, and anti-voltage gated K channel antibodies were negative. Infectious testing including blood culture, urine culture, CSF culture, and respiratory viral panel were negative. CSF HSV PCR, stool enterovirus, and serum parvovirus were negative. He was empirically treated for tickborne illnesses and later treated for a Citrobacter tracheitis starting on day 10 of hospitalization.

Initial MRI brain on day 3 was normal. Repeat MRI brain on day 10 showed symmetric restricted diffusion throughout both gray and white matter, specifically the bilateral frontal and medial temporal lobes, bilateral cingulate gyri, superior parietal lobes, basal ganglia, thalami, and internal capsules (Figure 1). Areas of restricted diffusion had an ADC correlate with associated T2 FLAIR hyperintensities. There was no contrast enhancement or SWI dropout visualized. MRA and MRV were unremarkable. MRI Spectroscopy showed decreased neuronal integrity with reduced N-acetylaspartate peaks. The MRI interpretation was most likely post-ictal edema in the setting of severe status epilepticus or less likely encephalitis. He received pulse steroids and IVIg for presumed MIS-C beginning day 4 with improvement in his seizures by day 7, was extubated, and discharged on day 25 to inpatient rehabilitation on levetiracetam and phenobarbital. He continued a steroid taper for an additional 4 weeks. He showed developmental regression and dysphagia requiring a gastrostomy tube but did not have recurrent seizures. Repeat neurologic exam showed limited interaction, no tracking, diffuse hypertonia, and clonus bilaterally.

Discussion

Patient presented with fever and seizures lasting several days without clear etiology suggestive of Febrile Infection Related

Table 2. Genetic Variants Identified via Invitae Epilepsy Panel.

Gene	Variant	Zygosity	
CACNA1H	c.433 G>A (p.Ala145Thr)	Heterozygous	Variant of Unknown Significance
MTOR	c.5897 G>A (p.Arg1966Gln)	Heterozygous	Variant of Unknown Significance
PCDH19	c.224A>G (p.Asn75Ser)	Hemizygous	Variant of Unknown Significance
RELN	c.4703 C>T (p.Ala1568Val)	Heterozygous	Variant of Unknown Significance
SCN1A	c.2057A>C (p.Glu686Ala)	Heterozygous	Variant of Unknown Significance

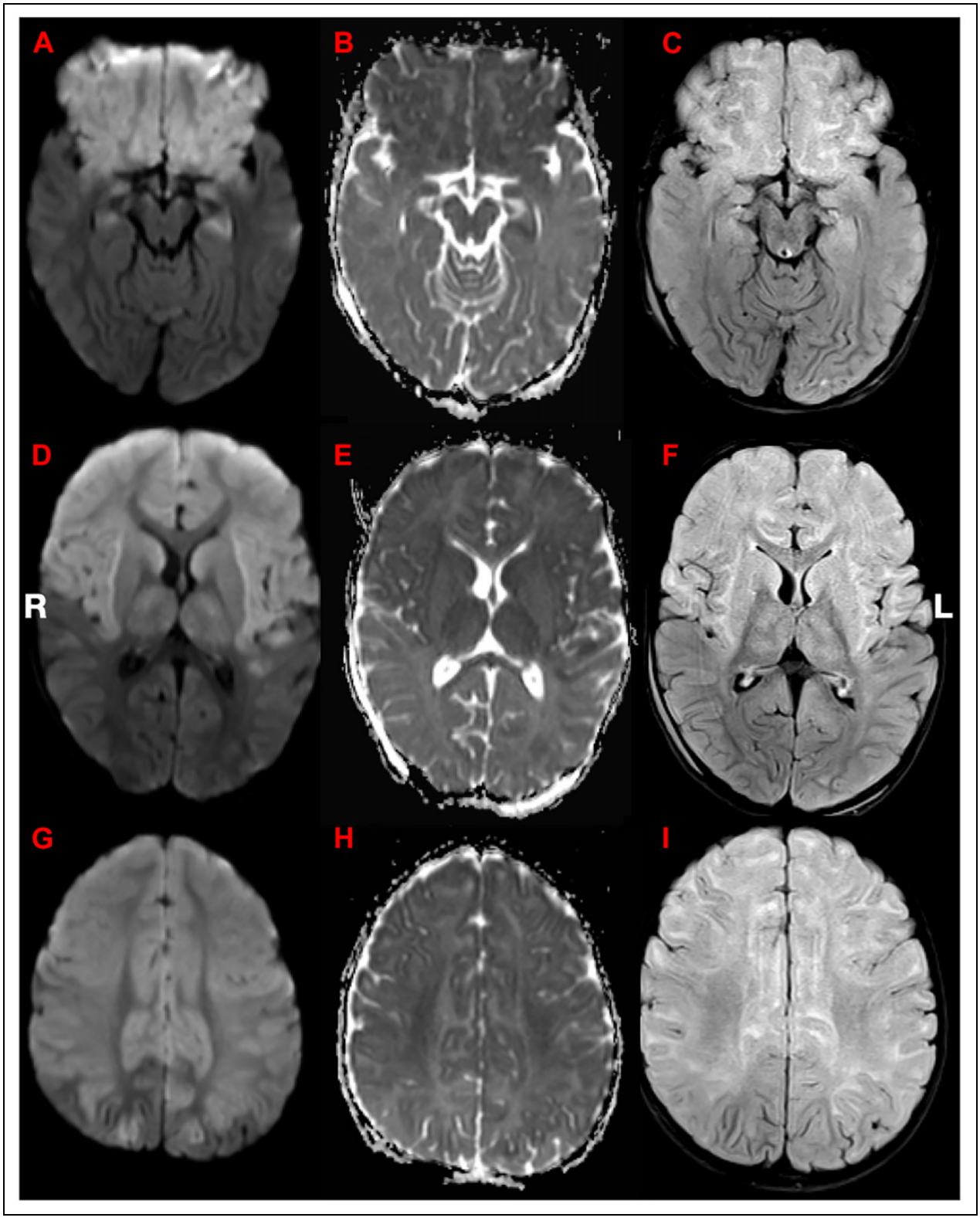

Figure 1. MRI brain with and without contrast. DWI sequence on day 10 shows symmetric restricted diffusion throughout both gray and white matter, specifically the bilateral frontal and medial temporal lobes, bilateral cingulate gyri, superior parietal lobes, basal ganglia, thalami, and internal capsules (A, D, G). Areas of restricted diffusion has associated ADC correlate (B, E, H) as well corresponding T2 FLAIR hyperintensities (C, F, I). There was no enhancement or SWI dropout visualized.

Epilepsy Syndrome (FIRES). The patient met clinical criteria for MIS-C with fever, labs consistent with inflammation (including elevated CRP, ESR, procalcitonin, d-dimer, ferritin, LDH, reduced lymphocytes, low albumin), multisystem organ involvement (cardiac, respiratory, hematologic, neurological), and positive COVID-19 IgG antibody. Although SCN1A and PCDH19 mutations are known to cause febrile epileptic syndromes including Dravet Syndrome, whether their phenotypic expressions occur depends on a variety of factors.[7] In this particular patient, as he is male, the PCDH19 variant is unlikely to be the cause of this clinical presentation. The variant in the SCN1A gene was inherited and determined to be unlikely to alter protein structure or be pathogenic. Given the atypical brain imaging, multi-organ pathology, and some improvement on pulse steroids and IVIg, it is reasonable to suspect COVID-19 and MISC were non-specific contributing factors to his clinical presentation.

Although he met the clinical criteria, his case is not typical for MIS-C based on his young age of 12 months, the pattern and severity of MRI brain findings, and poor neurologic outcome. More typical imaging findings are less extensive areas of T2 hyperintensity involving gray and white matter.[8] To date, there have been 935 cases of MIS-C worldwide.[5] There has been no report of specific associated genetic variations that may contribute to a more severe neurologic involvement in the Mennonite population. Although his epilepsy gene panel was non-diagnostic, this does not rule out the possibility of a homozygous genetic predisposition to his clinical presentation. Further testing, including whole exome sequencing and chromosomal microarray, may be helpful to clarify this.

Previous multicenter studies highlighting neurologic involvement in COVID-19 or MIS-C showed differences in clinical symptoms based on age, including more commonly status epilepticus in children less than 5 years old and anosmia/ageusia in adolescents 13-20 years old.[9–11] This is consistent with our patient findings based on his age of 12 months. One study conducted in Chile showed 77.7% of patients who had significant improvement in neurologic manifestations of COVID-19/MIS-C, with persistent dysguesia noted in 2/13 patients and another case series showed 55% of MIS-C patients clinically normal at the time of discharge with minimal residual symptoms.[8,12] In contrast, another multicenter study showed that while most patients had transient neurologic symptoms that resolved by the time of discharge, 12% of patients had severe neurologic morbidity with majority of these patients having death or neurologic disability at the time of discharge,[9] which highlights the wide range of outcomes following COVID-19 infection. Several case series and a recent multicenter study have demonstrated the heterogeneity of neurologic clinical and radiographic manifestations of MIS-C, and our case is an additional example of that.[2,8] Our patient continued to have progressive neurologic decline despite treatment with IVIG and pulse dose steroids, but did have improvement in seizure activity. The differential diagnosis of this clinical presentation includes FIRES, and MIS-C should be included when considering potential triggers for FIRES.

Author Contributions

HCA substantially contributed to conception or design, contributed to acquisition, analysis, or interpretation of data, drafted the manuscript, critically revised the manuscript for important intellectual content. AB substantially contributed to conception or design, contributed to acquisition, analysis, or interpretation of data, critically revised the manuscript for important intellectual content. SZM and HC critically revised the manuscript for important intellectual content. GM contributed to acquisition, analysis, or interpretation of data, critically revised the manuscript for important intellectual content, gave final approval. All the authors agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics and Informed Consent

Our institution does not require ethical approval for reporting individual cases or case series. Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Gayatra Mainali—Member of Data Monitoring Committee for Molybdenum Cofactor Deficiency—Origin Biosciences.

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