



Global Longitudinal Strain Reduction in the Absence of Clinical Cardiac Symptoms in Multisystem Inflammatory Syndrome in Children Associated with COVID-19: A Case Series

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Abstract

Multisystem inflammatory syndrome in children is a term that encompasses the systemic inflammation seen in children 4–6 weeks following COVID-19 infection. Cardiac involvement is common in this condition and can range from mild myocarditis to severe hypotension and cardiogenic shock, but not all patients display overt cardiac symptoms. We present three such patients who presented with a variety of systemic inflammatory symptoms but lacked apparent cardiac symptoms, and all had normal left ventricular ejection fraction but reduced global longitudinal strain (GLS). GLS is a cardiac tissue deformation index measured by Echocardiography to detect early changes in global function even before changes in ejection fraction are seen. We suggest this finding may indicate subclinical myocardial injury and stress the need for closer evaluation and follow-up for these patients as well as further research on both the short- and long-term effects of COVID-19 on cardiac function in the pediatric population.

Keywords Multisystem inflammatory syndrome in children · COVID-19 · Global longitudinal strain · Echocardiography · Cardiac magnetic resonance imaging

Introduction

What was first reported in March 2020 as a “Kawasaki-like” illness in children with COVID-19 in Bergamo, Italy is now better known as multisystem inflammatory syndrome in children (MIS-C) [1], a hyperinflammatory syndrome with multiorgan dysfunction typically occurring 4–6 weeks after infection. The Center for Disease Control (CDC) diagnostic criteria for MIS-C include fever for ≥ 24 h, elevated inflammatory markers in the blood, and clinically severe illness involving ≥ 2 organ systems and requiring hospitalization in patients < 21 years of age currently or recently diagnosed with COVID-19 [2].

Cardiac involvement is common and can range from mild myocarditis (the most common finding in the acute phase) to severe hypotension and cardiogenic shock. Left ventricular ejection fraction (LVEF) reduction and abnormalities in multiple echocardiographic parameters of cardiac tissue deformation have been reported in MIS-C patients with varying levels of cardiac symptoms, with reduced global longitudinal strain (GLS) being the strongest predictor of myocardial injury [3]. Here we present 3 cases of GLS reduction in MIS-C patients with preserved LVEF who lacked apparent cardiac symptoms and suggest its potential to indicate subclinical myocardial injury.

Case Presentation

Case 1: A 14-year-old previously healthy male presented with 2 days of right lower quadrant abdominal pain, nausea, diarrhea, loss of appetite, fevers (T_{\max} 103.3F), and chills. Admission laboratory tests were remarkable for an elevated CRP of 33.5 ($N: \leq 8$ mg/L), ALP of 223 ($N: 38$ –126 U/L), and a positive COVID-19 IgG antibody test (he had tested positive for COVID-19 6 weeks prior). A

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CT abdomen-pelvis was obtained which showed hepatomegaly/fatty liver and wall thickening of the ascending colon but no signs of appendicitis. As the patient's CRP increased, MIS-C was suspected. Additional labs were obtained significant for an elevated D-dimer of 759 ($N: \leq 232$ ng/mL), fibrinogen of 670 ($N: 120$ – 450 mg/dL), ferritin of 389 ($N: 20$ – 300 ng/mL), and ESR of 37 ($N: 0$ – 15 mm/hour) indicating inflammatory process and thrombocytopenia, with platelets reaching a low of 85 ($N: 175$ – $332 \times 10^3/\mu\text{L}$). Transthoracic echocardiogram (TTE) showed apical wall hypokinesis and a reduced GLS of -15.5 ($N: -22$) (Fig. 1). EKG showed shortened PR intervals and delta waves, consistent with Wolff-Parkinson-White (WPW) syndrome (for which he had a positive family history but had not been diagnosed himself). BNP and troponins were normal. The diagnosis of MIS-C was made and the patient was started on intravenous immunoglobulin (IVIG), steroids, and low-dose aspirin. Gradually, his thrombocytopenia and leukocytosis improved, CRP down trended (after reaching a max of 115.8), symptoms improved, and he was discharged home. At 4-week follow-up, he remained asymptomatic (although he had been refraining from exercise) and his labs had normalized, but a repeat TTE showed persistent apical wall hypokinesis and decreased GLS of -10 . Cardiac magnetic resonance imaging (CMR) and stress test have been ordered for further analysis and he is being continued on aspirin.

Case 2: A 6-year-old previously healthy male presented with 6 days of high fever ($T_{\text{max}} 104\text{F}$), nausea, vomiting, diarrhea, abdominal pain and 2 days of diffuse body rash, bilateral conjunctival injection, eyelid swelling, and lower extremity swelling. Admission labs were significant for an elevated ESR of 16 ($N: 0$ – 15 mm/hour), CRP of 202 ($N: \leq 8$ mg/L), procalcitonin of 26 (≤ 0.09 ng/mL), D-dimer of 2767 ($N: \leq 232$ ng/mL), ferritin of 1355 ($N: 20$ – 300 ng/mL), and a decreased platelet count of 94 ($N: 206$ – $369 \times 10^3/\mu\text{L}$). BNP was elevated at 296 ($N: \leq 100$ pg/mL) and troponins were negative. Both COVID PCR and IgG antibody tests were positive indicating prior infection; while the patient did not experience symptoms himself, members of his household had tested positive 4 weeks prior. EKG was normal and TTE showed a reduced GLS of -17.9 with no other abnormalities. A diagnosis of MIS-C was made and the patient was started on IVIG, solumedrol, and low-dose aspirin. His CRP and BNP began to decrease, platelet count increased, and overall symptoms improved. He was discharged home after a week-long admission. At 2-week follow-up, the patient remained asymptomatic. Repeat TTE at this time showed a slightly improved but persistently reduced GLS of -18.6 with no other abnormalities (Fig. 2).

Case 3: A 7-year-old previously healthy male presented with 5 days of fevers ($T_{\text{max}} 104\text{F}$), abdominal pain, and vomiting as well as 2 days of an erythematous macular rash with central clearing on the abdomen and bilateral lower

Fig. 1 GLS imaging for Case 1: Echocardiography and strain curves showing the left ventricular peak systolic longitudinal strain to be -164.31% , -174.26% , and -121.97% for A4C, A2C, and A3C views, respectively, and the average peak GLS to be -153.5% . A4C apical 4-chamber view, A2C apical 2-chamber view, A3C apical 3-chamber view

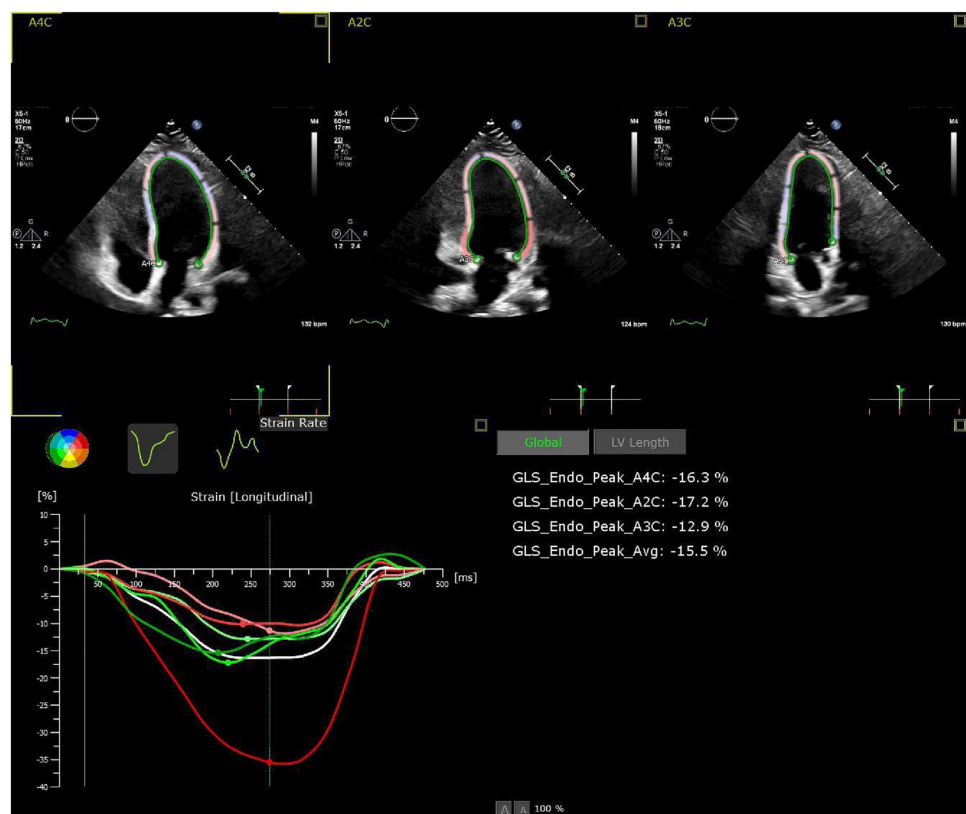
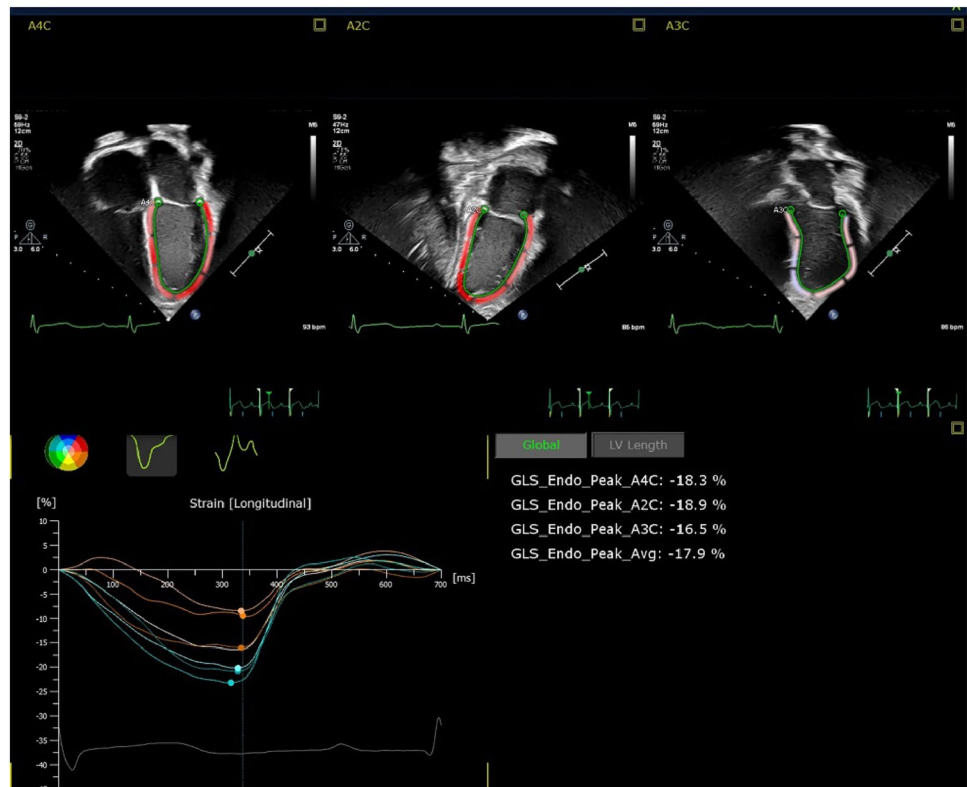


Fig. 2 GLS imaging for Case 2: Echocardiography and strain curves showing the left ventricular peak systolic longitudinal strain to be -1821.36% , -186.93% , and -168.50% for A4C, A2C, and A3C views, respectively, and the average peak GLS to be -178.96% . A4C apical 4-chamber view, A2C apical 2-chamber view, A3C apical 3-chamber view



extremities, bilateral conjunctival injection, eyelid swelling, and cracked lips. Admission labs were significant for an elevated CRP of 44 ($N: \leq 8$ mg/L), D-dimer of 933 ($N: \leq 232$ ng/mL), and a decreased albumin of 2.2 ($N: 3.5\text{--}4.8$ g/dL). BNP was mildly elevated at 185 ($N: \leq 100$ pg/mL) and troponins were negative. EKG and TTE were normal and right upper quadrant ultrasound showed mild hepatomegaly. COVID IgG test was positive; while the patient himself did not experience symptoms in the past, a member of his household had tested positive 4 weeks prior. A diagnosis of MIS-C was made and the patient was started on IVIG and steroids. His symptoms greatly improved, CRP down trended, and he was discharged home. At 4-week follow-up, the patient was asymptomatic; repeat EKG was normal while TTE showed a reduced GLS of -17.5 with trace mitral and tricuspid valve regurgitation (Fig. 3). He is being closely followed up for further monitoring of cardiac function.

Discussion

GLS is a parameter measured by speckle-tracking echocardiography, a technique that uses 2D imaging to evaluate both global and regional left ventricular systolic function [4]. It has recently gained popularity with studies showing it is a stronger and more reproducible measure of systolic function [5] than the traditional LVEF and is especially useful

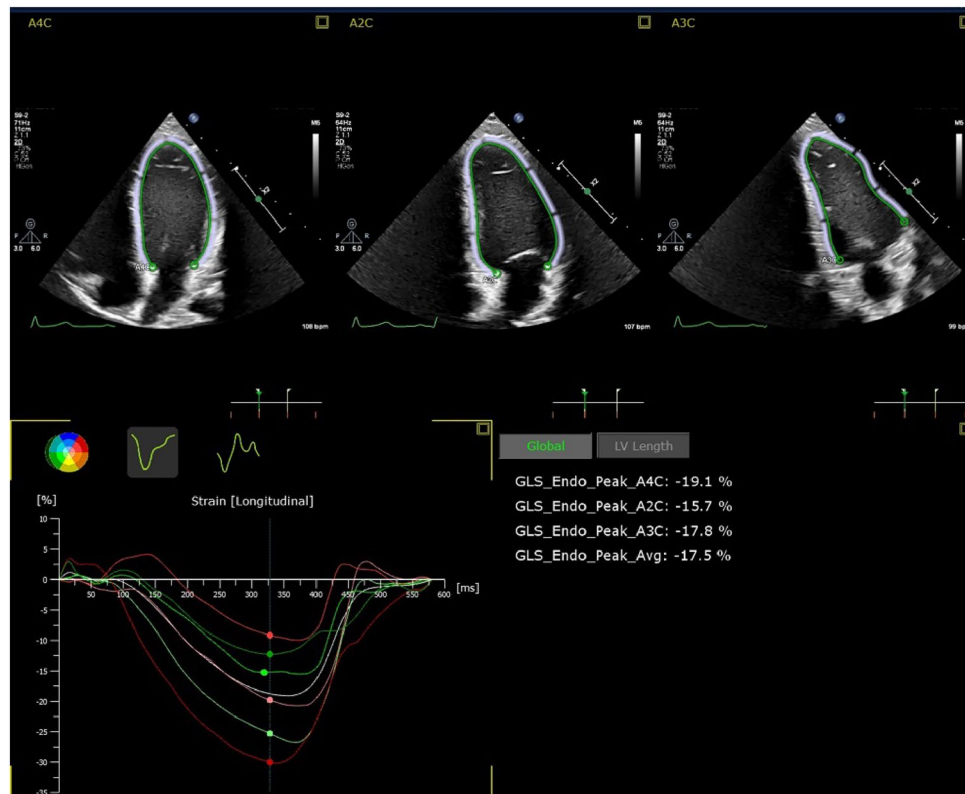
in detecting mild/subclinical cardiac dysfunction in patients with preserved LVEF [6]. A normal GLS value is approximately -22 .

While the literature on MIS-C is limited, a handful of studies have described patients with cardiac manifestations such as myocarditis, acute heart failure, or cardiogenic shock and reported abnormal echocardiographic parameters including GLS reduction (as is expected) [3, 7–9]. Matsubara et al. found GLS to be one of the strongest predictors of myocardial injury (as defined by increased BNP and troponins) in these patients along with global circumferential strain, peak left atrial strain, and peak longitudinal strain of the right ventricular free wall [3].

GLS reduction has not, however, been studied in MIS-C patients who lack overt cardiac symptoms, such as those in our study. Our cases presented with various systemic inflammatory symptoms but did not display signs of cardiac involvement such as profound hypotension, tachycardia, or dyspnea and had normal LVEF values, negative troponins, and unremarkable EKG tracings. Two patients had mildly elevated BNPs on admission and two showed wall motion/valvular abnormalities on TTE. All three patients had reduced GLS values which persisted (and in one case worsened) on follow-up 2–4 weeks after recovery.

Given the evidence showing GLS as a sensitive measure of ventricular dysfunction, we suggest that GLS reduction may indicate subclinical myocardial injury in these patients and/or

Fig. 3 GLS imaging for Case 3: Echocardiography and strain curves showing the left ventricular peak systolic longitudinal strain to be -1920.10% , -157.70% , and -175.87% for A4C, A2C, and A3C views, respectively, and the average peak GLS to be -17.56% . A4C apical 4-chamber view, A2C apical 2-chamber view, A3C apical 3-chamber view



predict oncoming cardiac symptoms and loss of LVEF. Further research is needed to better elucidate this relationship. A recent study in China of adult patients who had recovered from COVID-19 also reported reduced GLS values in those lacking cardiac symptoms during illness, similarly suggesting subclinical myocarditis caused by the virus [10]. Such a study in pediatric patients is warranted. It would be particularly beneficial to study children with elevated troponin levels in the setting of normal LVEF as well.

Although the clinical significance of this relationship is unknown, it is important for patients with asymptomatic GLS reduction to undergo further evaluation of cardiac function. We suggest CMR, which may detect features of myocarditis not found on TTE. Previous studies of viral myocarditis have shown that GLS (and other tissue deformation indexes) can independently predict ventricular dysfunction in patients with CMR-proven myocarditis and normal LVEF with high sensitivity and specificity [11]. Similarly, close follow-up and monitoring for worsening cardiac involvement is necessary for these patients after they recover from initial infection.

Conclusion

Pediatric patients with MIS-C secondary to COVID-19 who lack overt cardiac symptoms often have reduced GLS and other abnormalities in cardiac deformation parameters,

which may indicate subclinical myocardial injury. These patients would benefit from further evaluation and close follow-up to monitor cardiac function after recovery. As the pandemic continues, further research is needed to better understand the subclinical effects of COVID-19 on cardiac function both during and after initial infection.

Author Contributions SG created the study concept and design. SA performed data collection and wrote the manuscript. All authors commented on previous versions of the manuscript and approved the final manuscript.

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Data Availability The study data contain confidential patient information that does not allow it to be shared.

Declarations

Conflict of interest The authors have no conflict of interest to declare.

Consent to Participate Not required per institutional IRB.

Consent for Publication Not required per institutional IRB.

Ethical Approval This study was conducted in compliance with institutional ethical requirements.

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