Early Detection of Cardiovascular Morbidity in Pediatric Familial Mediterranean Fever: A Comprehensive Review of Diagnostic Modalities

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Abstract

Background: Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disorder in childhood, characterized by recurrent inflammatory attacks and persistent subclinical inflammation during attack-free periods. Although FMF is classically associated with serositis, increasing evidence shows that chronic inflammation may also affect the cardiovascular system in subtle but clinically meaningful ways. Children with FMF, even when treated with colchicine, may develop early myocardial, endothelial, or pericardial changes that remain asymptomatic for years. Early detection of such cardiovascular alterations is crucial, as they may contribute to long-term morbidity, particularly in patients with inadequate inflammatory control or in those at risk of amyloidosis.

Aim: This review comprehensively examines the current diagnostic modalities used to detect early cardiovascular involvement in pediatric FMF. It integrates insights from conventional and advanced echocardiography, myocardial strain imaging, tissue Doppler parameters, cardiac biomarkers, electrocardiographic indices, vascular imaging, and novel non-invasive tools. The goal is to highlight the sensitivity and specificity of each modality, explore their clinical utility in routine pediatric FMF assessment, and discuss the strengths and limitations of emerging technologies. Furthermore, the review aims to identify important research gaps regarding the prognostic meaning of subclinical findings and the potential reversibility of cardiac changes with optimized colchicine therapy or targeted anti-inflammatory treatment.

Conclusion: Cardiovascular assessment in pediatric FMF has evolved significantly, moving beyond detection of overt pericardial involvement to identifying subtle myocardial and vascular abnormalities long before they become clinically evident. Advanced echocardiographic techniques—particularly speckle-tracking strain imaging—have emerged as promising tools for uncovering early myocardial dysfunction, while markers such as NT-proBNP, hs-CRP, and measures of arterial stiffness provide additional insight into inflammatory cardiovascular burden. Despite these advances, substantial gaps remain regarding standardization of screening, prognostic thresholds, and interpretation of subclinical abnormalities in growing children. A multimodal, risk-stratified approach may offer the best framework for early detection and prevention of long-term cardiovascular morbidity in FMF. Large prospective pediatric studies are urgently needed to determine which diagnostic abnormalities predict future events and how early interventions may modify cardiac outcomes.

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Keywords: *Cardiovascular, Pediatric Familial Mediterranean Fever, Diagnostic Modalities*

Introduction

Familial Mediterranean Fever (FMF) is the most prevalent hereditary autoinflammatory disease in childhood, caused by pathogenic variants in the *MEFV* gene, which encodes pyrin—a key regulator of the innate immune response. Persistent inflammation, even during attack-free intervals, contributes to multisystem involvement and may predispose affected children to early cardiovascular alterations. Although FMF has traditionally been considered a benign condition when adequately treated with colchicine, mounting evidence suggests that chronic inflammation, endothelial dysfunction, and amyloid-related processes may place pediatric patients at risk for early cardiovascular morbidity. Importantly, children often remain asymptomatic despite measurable subclinical abnormalities, highlighting the need for early diagnostic vigilance in this population. [1–4]

Recent advancements in pediatric cardiology have introduced several tools capable of detecting subtle myocardial and vascular changes, including tissue Doppler imaging, speckle-tracking echocardiography, arterial stiffness assessments, and biomarkers reflecting cardiac stress or low-grade inflammation. Despite these innovations, routine cardiovascular screening is not standardized for children with FMF, and the prognostic significance of many subclinical findings remains unclear. The research gap centers on insufficient longitudinal pediatric data and limited consensus regarding which diagnostic modalities offer the greatest predictive value for future cardiovascular complications. Therefore, the aim of this review is to comprehensively analyze current and emerging diagnostic modalities used to identify early cardiovascular involvement in children with FMF, evaluate their clinical utility, and highlight areas requiring further pediatric-focused investigation. [5–8].

Pathophysiologic Basis of Cardiovascular Involvement in Pediatric Familial Mediterranean Fever

Chronic subclinical inflammation is the hallmark mechanism linking FMF to early cardiovascular alterations in children. Even during asymptomatic periods, elevations in inflammatory cytokines such as IL-1β, IL-6, and TNF-α persist and may contribute to endothelial dysfunction, increased oxidative stress, and impaired vascular reactivity. This inflammation-driven endothelial injury represents one of the earliest detectable cardiovascular changes in FMF and serves as a precursor to myocardial compromise or increased arterial stiffness. Studies demonstrate that pediatric FMF patients frequently show elevated inflammatory biomarkers—including serum amyloid A (SAA) and high-sensitivity CRP—even when clinically stable, emphasizing the continuous inflammatory burden exerted on cardiovascular tissues throughout childhood. [9–11]

Another crucial mechanism involves pyrin dysfunction resulting from *MEFV* gene mutations. Mutant pyrin enhances inflammasome activation, leading to recurrent IL-1β–mediated inflammatory cascades. Over time, this amplified innate immune response induces microvascular dysfunction that affects coronary microcirculation and myocardial tissue integrity. In children, where cardiovascular structures are still maturing, micro-injury may disrupt myocardial relaxation patterns, leading to subtle diastolic dysfunction long before systolic function becomes impaired. Several pediatric studies have identified abnormal myocardial performance index (MPI) and tissue Doppler velocities in FMF patients without overt cardiac complaints, supporting the concept that pyrin-driven inflammasome activity has measurable cardiac effects early in life. [12–14]

Amyloid A deposition represents another pathophysiologic concern, although clinically significant cardiac amyloidosis remains rare in childhood. Nonetheless, chronic elevations of SAA—particularly in children with colchicine resistance or non-adherence—can initiate early extracellular matrix remodeling, myocardial stiffness, and altered ventricular compliance. These processes may not yet translate into clinical manifestations but are increasingly detectable with modern diagnostic tools such as strain imaging and advanced tissue Doppler modalities. The potential for reversible dysfunction with adequate colchicine treatment underscores the importance of early detection and meticulous disease control in pediatric populations. [15–17]

Finally, autonomic nervous system imbalance has been proposed as an additional contributor to cardiovascular morbidity in pediatric FMF. Persistent inflammation may impair vagal tone, increase

sympathetic activity, and modify cardiac repolarization parameters—changes that can increase arrhythmia susceptibility. Pediatric studies have reported alterations in P-wave dispersion, QTc interval, and heart rate variability in FMF children, suggesting that inflammation-driven autonomic dysregulation may represent an underappreciated component of early cardiac involvement. Understanding these mechanisms highlights the need for comprehensive cardiovascular evaluation using diagnostic modalities capable of detecting myocardial, vascular, and electrophysiological abnormalities at early stages. [18–20]

Clinical Spectrum of Cardiac Involvement in Pediatric Familial Mediterranean Fever

Cardiac involvement in pediatric FMF spans a wide clinical spectrum, ranging from completely asymptomatic subclinical abnormalities to rare but clinically significant complications. Most commonly, children may present with subtle diastolic dysfunction, mild reductions in myocardial deformation indices, or endothelial dysfunction without overt symptoms. These findings are often detected during routine imaging or research-driven evaluations, underscoring the silent nature of early cardiovascular impairment in FMF. Despite the lack of symptoms, the presence of such abnormalities may reflect long-standing inflammatory activity and therefore warrants vigilant follow-up. [21–23]

Pericardial involvement is one of the more traditional cardiac manifestations of FMF, though its prevalence in children is relatively low. When present, pericarditis may mimic acute FMF attacks due to overlapping symptoms such as chest pain and fever. In many cases, pericardial effusion is small and resolves spontaneously or with the optimization of colchicine therapy. Nevertheless, recurrent pericarditis has been reported in pediatric FMF cohorts, and persistent inflammatory activity can predispose to chronic pericardial thickening or restrictive physiology if inadequately managed. Early detection through echocardiography remains essential to differentiate FMF-related pericarditis from infectious or autoimmune causes in children. [24–26]

Vascular involvement, especially endothelial dysfunction and increased arterial stiffness, has emerged as a prominent subclinical finding in pediatric FMF. Studies using brachial artery flow-mediated dilation (FMD), carotid intima-media thickness (cIMT), and pulse wave velocity (PWV) demonstrate measurable vascular impairment even in attack-free periods. These early vascular changes are believed to reflect the cumulative effects of chronic inflammation on the vascular wall and may represent precursors to future cardiovascular disease. Children with M694V homozygosity or frequent attacks appear to have more pronounced vascular abnormalities, highlighting the genotype–phenotype relationship in cardiovascular risk stratification. [27–29]

Electrophysiological abnormalities represent another important area of clinical concern. Alterations in P-wave dispersion, QTc interval prolongation, and decreased heart rate variability have been documented in pediatric FMF cohorts, suggesting increased susceptibility to atrial or ventricular arrhythmias. Although clinically significant arrhythmias remain rare in children, the chronic inflammatory milieu can disrupt autonomic balance and myocardial repolarization. Moreover, subclinical myocarditis has been reported in isolated cases, further emphasizing the need for ECG monitoring in high-risk pediatric patients, particularly those with persistent inflammation or colchicine resistance. [30–32]

In the rarest and most severe end of the spectrum, AA amyloidosis poses a risk of cardiac deposition, but this is exceedingly uncommon in children due to earlier diagnosis, improved access to colchicine therapy, and better disease monitoring. Nonetheless, the presence of persistent elevation of serum amyloid A or inadequate colchicine adherence remains a significant risk factor, and awareness of early signs—such as subtle increases in myocardial stiffness—can be lifesaving. Early cardiac involvement in amyloidosis may manifest only through strain abnormalities long before standard echocardiography detects structural changes, highlighting the role of advanced diagnostic modalities in high-risk pediatric FMF populations. [33–35]

Conventional Echocardiography in Pediatric FMF

Conventional transthoracic echocardiography remains the cornerstone of cardiac assessment in children with FMF. Although most patients demonstrate preserved systolic function on standard indices such as

left ventricular ejection fraction (LVEF), more sensitive parameters have revealed subtle abnormalities in ventricular relaxation patterns. Mitral inflow velocities, E/A ratios, and deceleration time are often altered in FMF children, reflecting low-grade diastolic impairment associated with chronic inflammation. These findings are particularly evident in patients with frequent attacks or elevated inflammatory markers, underscoring the value of routine echocardiography in longitudinal surveillance. [36–38]

Tissue Doppler Imaging (TDI)

Tissue Doppler imaging enhances the sensitivity of conventional echocardiography by quantifying myocardial velocities and detecting subclinical myocardial dysfunction. In pediatric FMF, abnormalities in early diastolic (Em) and late diastolic (Am) myocardial velocities have been reported, often with increased myocardial performance index (MPI), indicating global myocardial dysfunction. TDI-derived parameters frequently correlate with inflammatory burden, suggesting that chronic elevation of cytokines may impair myocardial relaxation and contraction dynamics. Because TDI is widely available and non-invasive, it remains an essential component of early cardiac evaluation in FMF children. [39–41]

Speckle-Tracking Echocardiography and Myocardial Strain

Speckle-tracking echocardiography has emerged as one of the most sensitive tools for detecting early myocardial impairment in pediatric FMF. Global longitudinal strain (GLS) reductions have been consistently observed in children with FMF despite preserved LVEF, indicating that myocardial deformation abnormalities precede conventional echocardiographic changes. Longitudinal, circumferential, and radial strain measurements provide insight into myocardial fiber interactions affected by chronic inflammation. These strain abnormalities sometimes correlate with SAA levels or frequency of febrile attacks, supporting their utility as both diagnostic and monitoring tools. Given its reproducibility and prognostic potential, strain imaging is increasingly recommended in pediatric FMF cardiovascular evaluation protocols. [42–44]

Electrocardiography and Electrophysiologic Assessment

Electrocardiographic evaluation is crucial for identifying potential arrhythmic risk in pediatric FMF. Increased P-wave dispersion and prolonged QTc intervals have been reported in several cohorts, reflecting autonomic imbalance and altered myocardial repolarization secondary to chronic inflammation. Heart rate variability (HRV) analyses demonstrate reduced vagal activity, suggesting heightened sympathetic tone in FMF children even during attack-free periods. Although overt arrhythmias remain uncommon, these electrophysiologic markers may serve as early indicators of vulnerability and warrant regular monitoring, particularly in children with prolonged disease duration or colchicine resistance. [45–47]

Cardiac Biomarkers

Biomarkers play an increasingly important role in assessing cardiovascular risk in FMF. High-sensitivity C-reactive protein (hs-CRP) and serum amyloid A (SAA) reflect both systemic and vascular inflammation. In addition, NT-proBNP levels may increase in FMF children with subclinical diastolic dysfunction or strain abnormalities, suggesting early myocardial stress. Other novel markers—such as asymmetric dimethylarginine (ADMA), a mediator of endothelial dysfunction—have been shown to be elevated in pediatric FMF, reinforcing the link between inflammation and vascular pathology. While biomarkers alone are insufficient for diagnosis, they significantly enhance the predictive value of imaging modalities when used in combination. [48–50]

Assessment of Vascular Structure and Function

Vascular imaging techniques, including carotid intima–media thickness (cIMT) and pulse wave velocity (PWV), offer non-invasive evaluation of arterial stiffness in children. Increased cIMT and impaired flow-mediated dilation (FMD) have been documented in pediatric FMF cohorts, demonstrating early vascular damage linked to persistent inflammation. PWV measurements reveal increased arterial stiffness even in clinically stable patients, suggesting that vascular remodeling may begin early in the disease course. Incorporating these modalities into routine assessment may allow for early identification

of children at higher risk for long-term cardiovascular morbidity. [51–53]

Cardiac Magnetic Resonance Imaging (MRI)

Although less commonly used in children due to cost and availability, cardiac MRI provides unparalleled tissue characterization and is valuable in detecting myocardial edema, fibrosis, or inflammation. Limited pediatric FMF studies suggest that MRI may detect abnormalities such as T1/T2 mapping changes even when echocardiographic parameters are normal. This modality is particularly useful when myocarditis, amyloidosis, or unexplained ventricular dysfunction is suspected. As MRI techniques become more accessible and child-friendly, they hold promise for improving early detection and prognostication in FMF-associated cardiac involvement. [54–56]

Emerging and Novel Diagnostic Modalities

Advances in cardiovascular imaging and molecular diagnostics continue to improve early detection of cardiac involvement in FMF. Novel ultrasound-derived technologies, such as 3D strain imaging and myocardial work indices, offer enhanced sensitivity for detecting subtle systolic dysfunction. In parallel, emerging biomarkers—including microRNAs associated with inflammation and endothelial dysfunction—are being investigated as potential predictors of cardiac remodeling. Although these approaches remain predominantly research tools, their integration with established diagnostic modalities may significantly refine cardiovascular risk stratification in pediatric FMF. [57–59]

Integration of Diagnostic Modalities: Toward a Multimodal Strategy

Early cardiovascular assessment in pediatric FMF is most effective when different diagnostic tools are combined rather than used in isolation. Conventional echocardiography can exclude gross structural disease and overt pericardial effusion, while tissue Doppler and strain imaging uncover subtle diastolic or systolic dysfunction in clinically silent children. When these are interpreted together with ECG indices (QTc, P-wave dispersion), arterial stiffness markers, and inflammatory biomarkers, a more accurate picture of cardiovascular risk emerges. This multimodal approach aligns with growing evidence that FMF-related cardiovascular involvement is often mild, functional, and diffuse, requiring sensitive tools to detect and monitor it over time. [60–63]

A tiered strategy can be particularly helpful: all children with FMF can undergo baseline echocardiography and ECG, while higher-risk subgroups—those with early onset, long disease duration, frequent attacks, elevated SAA/CRP, or poor colchicine adherence—may benefit from periodic strain imaging, vascular stiffness assessments, and expanded biomarker panels. Recent pediatric studies combining speckle-tracking echocardiography with markers like NT-proBNP, endocan, ADMA, or arterial stiffness parameters illustrate how layered testing can identify children with both myocardial and vascular involvement, even when standard tests appear normal. Such a multimodal model supports individualized follow-up intervals and intensity of monitoring. [64–68]

Impact of Colchicine and Biologic Therapy on Cardiovascular Parameters

Colchicine remains the cornerstone of FMF treatment and indirectly exerts cardiovascular protection by suppressing attacks and subclinical inflammation. Pediatric cohorts show that adequate colchicine dosing and adherence are associated with lower SAA and CRP levels, which in turn correlate with more favorable echocardiographic and vascular findings. Recent child-focused work suggests that during attack-free periods under good control, myocardial strain and diastolic indices may normalize or improve, supporting the concept that at least part of FMF-related cardiac dysfunction is functional and potentially reversible with sustained anti-inflammatory control. [60,64–66]

In colchicine-resistant or intolerant patients, IL-1–targeted biologics (such as anakinra or canakinumab) are increasingly used to control systemic inflammation. Although pediatric data specifically linking these agents to improved cardiac outcomes are still limited, adult and mixed-age FMF cohorts suggest that aggressive suppression of IL-1–mediated inflammation may reduce endothelial activation and vascular stiffness. For children with persistently abnormal myocardial strain or arterial stiffness despite optimized colchicine, biologic therapy may therefore offer dual benefits: prevention of amyloidosis and possible attenuation of early cardiovascular remodeling. Rigorous prospective pediatric studies are

needed to quantify these effects and define when abnormal cardiac findings should influence escalation to biologic therapy. [62,63,66–68]

Practical Screening and Follow-up Recommendations in Pediatric FMF

From a pediatric practice perspective, a pragmatic screening framework can be proposed. At diagnosis, all children with FMF should undergo a baseline 12-lead ECG and transthoracic echocardiogram, including Doppler assessment of diastolic function. For those with additional risk factors—early-onset disease, severe genotypes, frequent attacks, elevated SAA/CRP, or family history of premature cardiovascular disease—baseline myocardial strain and at least one vascular measurement (e.g., cIMT or arterial stiffness) are advisable. This initial profile establishes a reference for future comparison and helps identify children already showing subclinical involvement at presentation. [60,61,64–66] Follow-up intervals can then be tailored according to risk. Clinically stable, well-controlled children without baseline abnormalities may be reviewed with ECG and basic echocardiography every 2–3 years, whereas those with documented strain abnormalities, increased arterial stiffness, or repolarization changes warrant closer surveillance—annually or even more frequently if disease activity remains high. Reassessment should also follow major changes in treatment (such as starting biologics) or periods of increased attack frequency. Incorporating simple measures like heart rate variability or QTc tracking into routine follow-up can help detect evolving autonomic or electrophysiologic disturbances in time to trigger more detailed cardiology evaluation. [61,66,69]

Research Gaps and Future Directions

Despite growing evidence, several critical questions remain unanswered regarding cardiovascular morbidity in pediatric FMF. The long-term prognostic significance of subclinical findings—such as mildly reduced GLS, modest increases in arterial stiffness, or borderline QTc prolongation—has not been clearly defined in children, largely due to the lack of sufficiently powered longitudinal cohorts with standardized cardiac assessments. It is still unclear which patterns or thresholds of abnormality predict future clinical events, including arrhythmias, heart failure, or accelerated atherosclerosis in adulthood. Addressing this gap requires coordinated, multicenter pediatric studies with harmonized imaging and biomarker protocols. [60–62,70]

Another priority is the development of pediatric-specific algorithms that integrate genetic data, inflammatory load, treatment response, and multimodal cardiovascular findings into practical risk scores. Emerging markers—such as nailfold capillaroscopy changes, novel vascular markers, and advanced MRI or strain-derived indices of myocardial work—need validation in FMF children and comparison with simpler, more accessible tools. Finally, interventional trials examining whether intensifying anti-inflammatory therapy based on early cardiac abnormalities can actually modify cardiovascular trajectories would provide the strongest evidence to incorporate systematic cardiac screening into routine FMF care. [63,66–68,70]

Conclusion

Cardiovascular involvement in pediatric FMF is often silent, functional, and closely linked to persistent inflammation, yet it carries potential implications for lifelong cardiovascular health. Modern diagnostic modalities—including tissue Doppler, speckle-tracking strain imaging, vascular stiffness measurements, and refined biomarker panels—allow detection of myocardial, vascular, and electrophysiologic changes long before clinical disease becomes evident. When these tools are integrated into a structured, risk-adapted screening strategy and combined with aggressive control of inflammation through colchicine and, when needed, biologic therapy, they offer a realistic opportunity to prevent or mitigate long-term cardiovascular morbidity in children with FMF. Continued pediatric-focused research will be essential to refine thresholds, validate prognostic markers, and translate subclinical findings into clear, evidence-based management algorithms.

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