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Clinical Utility of Follow-up Echocardiograms in Uncomplicated Kawasaki Disease

Shaila Siraj[1], Carlos Sanchez Parra[2], Jasmine Jordan[3], Ashish Shah[4], Ernest Amankwah[5], Jeffrey Fadrowski[6]

[1]Division of Pediatric Hospital Medicine, Johns Hopkins All Children's Hospital, St. Petersburg, United States

[2]Department of Internal Medicine and Pediatrics, University of South Florida, Tampa, United States

[3]Department of Pediatrics, University of South Florida, Tampa, United States

[4]Division of Pediatric Cardiology, Johns Hopkins All Children's Hospital, St. Petersburg, United States

[5]Division of Pediatric Oncology, Johns Hopkins All Children's Hospital, St. Petersburg, United States

[6]Division of Pediatric Nephrology, Johns Hopkins University, Baltimore, United States

Email address:

Ssiraj2@jhmi.edu (S. Siraj)

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Abstract: Kawasaki Disease (KD) is the leading cause of acquired heart disease among children in the developed world. Consensus-based guidelines from the American Heart Association (AHA) recommend echocardiograms be performed at the time of diagnosis, at two weeks, and again at 4-6 weeks for uncomplicated KD. This study examines the frequency of cardiac abnormalities on follow-up echocardiograms in patients with uncomplicated KD. We performed a retrospective chart review using the electronic health record at a tertiary care freestanding children's hospital, non-KD referral center. Patients with KD hospitalized from 1/1/2005 to 10/31/2016 were screened for uncomplicated disease (defined as normal echocardiogram upon diagnosis and fever resolution with initial therapy). Ninety-four patients with uncomplicated KD were included in this study. Fifty-seven percent were male, and the median age was 2.6 years (range=0.15-12). Fifty patients had an echocardiogram performed at two weeks, revealing no (0%) coronary abnormalities. Fifty-six patients had an echocardiogram performed at 6-8 weeks, revealing no coronary anomalies (0%). This study revealed that patients with uncomplicated KD did not develop coronary abnormalities on follow-up echocardiograms, providing additional evidence to help inform current KD guidelines. Further studies are needed to evaluate the optimal frequency of recommended echocardiograms for patients with uncomplicated KD.

Keywords: Kawasaki Disease, Echocardiography, Pediatric Cardiology, Hospital Medicine

1. Introduction

Kawasaki Disease (KD) is the leading cause of acquired heart disease in children in the United States [1, 2]. Previously referred to as Mucocutaneous Lymph Node Syndrome, KD is a small to medium vessel vasculitis that, if left untreated, can result in coronary abnormalities in up to 15-25% of patients [3]. Complications if left untreated include coronary stenosis, coronary calcification, diastolic dysfunction, myocardial infarction, and sudden death [13]. Intravenous immunoglobulin in combination with aspirin is known to significantly decrease new coronary artery abnormalities at thirty days [15]. Furthermore, when administered during the acute phase of illness (within ten days of fever), it has been shown to reduce the risk of coronary abnormalities to less than 5% [1, 4, 5].

The concept of risk stratification was introduced in the first consensus-based American Heart Association (AHA) guidelines for the long-term management of patients with KD [1]. In these guidelines, Risk Level 1 patients were described as those without coronary artery changes at any stage of illness [1]. They, therefore, did not require monitoring beyond the first year unless cardiac disease was suspected [1]. These recommendations were reaffirmed in

the 2004 guidelines; however, it was cautioned that because the future risk for ischemic heart disease in this category of patients was still undetermined, periodic assessment and counseling on cardiovascular risk factors should occur every five years [2]. The most updated guidelines in 2017 further specified that when coronary arteries remain below a Z-score of 2, patients could be considered for discharge from practice from future cardiology evaluations at 4-6 weeks [6]. Currently, patients with uncomplicated KD (defined as normal echocardiogram upon diagnosis and fever resolution with initial therapy) require a minimum of 3 echocardiograms: at the time of diagnosis, at 1-2 weeks, and 4-6 weeks after diagnosis.

Only a few studies provide evidence to help inform the American Heart Association guideline recommendations regarding the value of repeated echocardiograms in children with an uncomplicated course of KD. In a study performed by Dominguez et al., up to 80% of patients with significant coronary abnormalities on follow-up echocardiograms had some abnormality evident on the initial baseline echocardiogram [7]. In a retrospective chart review of patients with KD, Scott et al. examined whether the third echocardiogram performed six months to 1 year after the onset of KD identified any case of coronary artery abnormalities when previous echocardiograms were normal [8]. Of 50 children with normal echocardiogram findings between 2 weeks and two months, none were found to have echocardiogram abnormalities in later studies [8]. In 2005, Lee et al. studied a cohort of 176 patients and determined that no patient who had normal echocardiographic findings at 1-2 months developed subsequent abnormalities [5]. These findings supported Scott et al.'s study and suggested that additional echocardiographic studies beyond eight weeks for coronary artery morphology are unnecessary if previous studies have been normal [5]. Recently, a study published by de Ferranti et al. reported the findings of repeated echocardiograms in patients with uncomplicated KD and initially normal echocardiograms. In this study, 8/464 (1.7%) patients developed subsequent abnormalities in follow-up echocardiograms [9]. They concluded that a 6-week echocardiogram might be unnecessary for patients with uncomplicated cases of KD with normal coronary arteries at baseline and 2 weeks [9]. To our knowledge, de Ferranti's study is the first to investigate the utility of obtaining a 6-week echocardiogram in patients with uncomplicated KD. However, the authors mentioned that their findings have limited generalizability because they represent a large referral center for KD [8].

Ming-Tai et al. reported that giant coronary aneurysm severity one month after onset was the most crucial factor for persistence, with all giant aneurysms persisting long term [14]. Given the consequences of missed coronary abnormalities in patients with KD, it is critical to confirm these results in other settings. This study aims to determine the likelihood of coronary abnormality development on subsequent imaging in patients with uncomplicated KD in a non-referral center when all other echocardiograms have been normal in order to help inform best practice for follow-up.

2. Methods

2.1. Patient Selection

This study is a retrospective chart review using the electronic health record (EHR, Cerner) at a freestanding, tertiary care pediatric, non-KD referral center. Patients hospitalized from 1/1/2005 to 10/31/2016 with KD were identified by screening for the corresponding ICD-9 (446.1) and ICD-10 (M30.3) discharge diagnoses. The details of each inpatient stay were reviewed, including the admission history and physical report, daily progress notes, and discharge summaries, allowing for the identification of patients eligible for our study based on the inclusion criteria listed below.

2.2. Inclusion / Exclusion Criteria

Patients were included in this study if they were hospitalized with uncomplicated KD (fever resolved with initial therapy and had no coronary abnormalities, defined as all measured coronary diameters with $Z < 2.0$ on echocardiogram, and had additional echocardiograms performed). Patients with complicated KD were excluded from this study. Patients were considered to have complicated KD if they met any of the following criteria: coronary abnormalities on echocardiogram at time of diagnosis, persistence of fever >48 hours after initial treatment with IVIG, or treatment with multiple doses of IVIG or a second-line agent (i.e., steroids, rituximab). Coronary abnormalities were defined per AHA guidelines as one of the following: Z score of left anterior descending (LAD) or right coronary artery (RCA) >2.0, coronary arteries met Japanese Ministry of Health criteria for aneurysms, or three other suggestive features exist, decreased LV function, mitral regurgitation, pericardial effusion, or Z scores in LAD or RCA of >2.0 (considered coronary artery dilatation) [6]. Patients who did not have more than one echocardiogram for review were also excluded as we could not confirm follow-up elsewhere. Additional information, including age, gender, ethnicity, race, weight, BMI, insurance, and complete versus incomplete KD data, were collected. Data were extracted from the electronic medical record with a case report form and entered into a REDCap database (Vanderbilt University, Tennessee, USA).

2.3. Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical data. Age was summarized using median and range, and the categorical variables were summarized using counts and percentages. All analyses were performed using SAS version 9.4.

3. Results

A total of 235 patient charts were reviewed. Of these, 109

patients were excluded because they had complicated KD. Our study's most common reasons for complicated disease were abnormal coronary arteries (Z score >2.0) on initial echocardiogram and retreatment with IVIG and steroids. Of the 126 patients identified as having uncomplicated KD, 32 had only one echocardiogram in the EHR and were excluded due to lack of follow-up. This left 94 patients with uncomplicated KD who had additional follow-up echocardiograms and thus were included in this study (Figure 1). Fifty-seven percent were male, and the median age was 2.6 years (range=0.15-12). Fifty patients had an echocardiogram performed at two weeks, which revealed no coronary abnormalities (0%). Fifty-six patients had an echocardiogram performed at 4-6 weeks, which again revealed no coronary abnormalities (0%). Fifty patients had additional echocardiograms performed after six weeks, none of which revealed abnormalities (0%). Of the 94 patients included in this study, 29 (31%) received guideline-based follow-up with echocardiograms performed at both weeks and at 4-6 weeks (Figure 2).

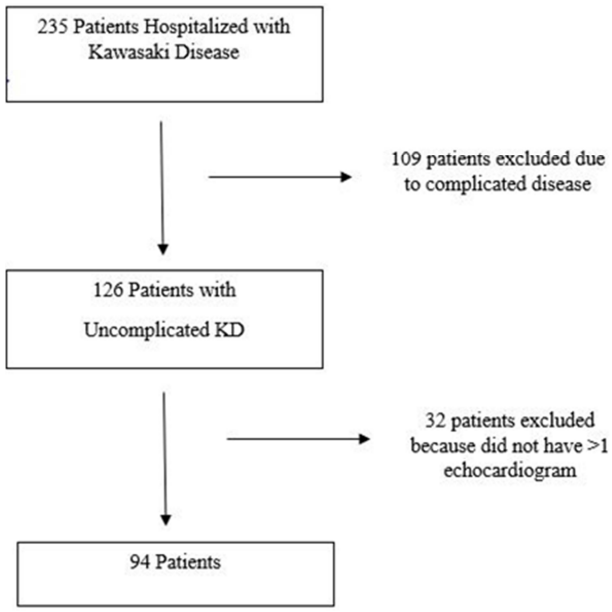

Figure 1. *Inclusion/Exclusion Criteria Chart.*

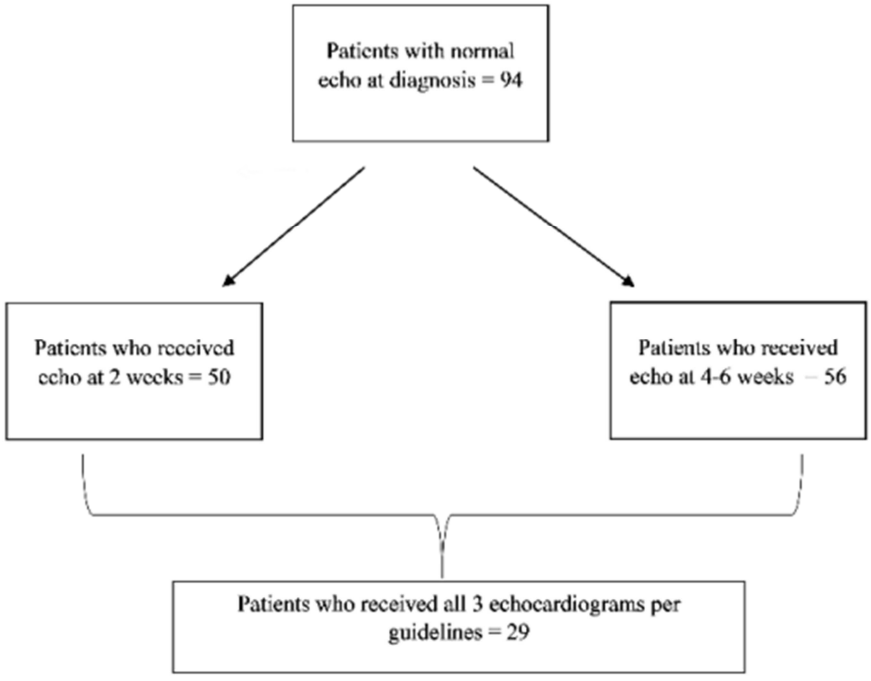

Figure 2. *Follow-up Echocardiograms.*

4. Discussion

In this retrospective, descriptive cohort study of 94 patients with uncomplicated KD, no patients developed coronary aneurysms on follow-up echocardiograms. Our findings are similar to the results from de Feranti's recently published paper [9]. In that study, among patients with initially normal echocardiograms, only 8/464 (1.7%) had abnormalities on subsequent imaging. Seven of these patients had normal echocardiograms by the 6-week visit. The remaining patient had minimal dilation at six weeks of the right coronary artery (Z score of 2.1). There were no additional echocardiograms available for review for that patient to verify resolution.

There are several reasons to support the frequency of echocardiograms recommended by the AHA. At the 2-week cardiology visit, the patient is assessed for reoccurrence of fever or any concerning clinical symptoms, adherence to aspirin therapy, and an echocardiogram screens for coronary abnormalities. In this acute phase of KD, new abnormalities on echocardiogram may impact recommended anticoagulation therapies [9]. For example, if a patient develops medium-sized coronary artery dilation with a Z score >5 to <10, with an absolute luminal dimension of <8mm, dual-antiplatelet

therapy of aspirin plus clopidogrel can be considered [11]. In addition, low Molecular Weight Heparin can be considered an option for chronic thromboprophylaxis for patients with large or giant coronary artery aneurysms, particularly for young infants or those with expanding aneurysms early in the course of their illness [6]. However, there is limited information on the frequency of the development of these abnormalities in uncomplicated KD patients with initially normal echocardiograms.

The rationale for performing the echocardiogram at 4-6 weeks is to follow clinical progress beyond the acute phase of illness and provide objective data to inform the decision to discontinue low-dose aspirin therapy. De Ferranti acknowledged that the 6-week echocardiogram maximizes the sensitivity of the detection of additional coronary abnormalities. However, based on the very low prevalence of detecting new abnormalities beyond the acute phase of illness, this additional echocardiogram might be eliminated from a cost-benefit standpoint.

Because healthcare expenditure is at an all-time high, cost-consciousness is an important consideration when making recommendations for the standard of care. An average transthoracic echocardiogram costs up to $2,000 [10]. This does not include the fees for follow-up care by the cardiologist or the costs of sedation for patients, unpaid workdays, and travel costs, representing a significant burden for families. However, the consequence of missing a cardiac abnormality in the setting of KD could be potentially severe. Given the above, and as current guidelines remain largely opinion-based, it is important to inform the utility of the current frequency of echocardiograms recommended for uncomplicated KD with studies such as this one. Further studies which help stratify the risk of patients with KD, thus informing intensity of follow-up care, are needed.

There are several limitations to this study. First, a significant proportion of patients with uncomplicated KD did not have the recommended number of echocardiograms as recommended by AHA guidelines, limiting the sample size. Second, there is a possibility that these patients received follow-up care at various surrounding community pediatric cardiology practices in the Tampa Bay Area, and we did not capture all follow-up. The variability in echocardiogram surveillance with lack of proper follow-up has been described in the literature as a problem at other non-referral centers for KD [11, 12].

5. Conclusions

This study revealed that no patients with uncomplicated KD had coronary abnormalities on follow-up echocardiograms, further informing AHA guidelines regarding the optimal echocardiogram follow-up frequency in patients with uncomplicated KD. For uncomplicated KD patients, there may be little clinical utility in performing multiple, repeated echocardiograms. A systematic and thorough institutional approach to coordination of care is vital regardless of the timing of echocardiograms, particularly in settings where patients have multiple options for care. Future research should examine if this study's findings can be replicated in a larger patient population including community hospitals. In addition, more studies are needed to further risk-stratify patients with KD and guide new guidelines for the frequency of echocardiogram follow-up.

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