ARC Journal of Radiology and Medical Imaging
Volume 3, Issue 1, 2018, PP 7-11
www.arcjournals.org

Cardiac Imaging in Kawasaki Disease

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Abstract: *Kawasaki disease (KD) is an acute systemic vacuities syndrome occurring mostly in children aged 6 months-5 years. Development of coronary artery aneurysms (CAA) is the most important and widely recognized complication of KD. It confirms the diagnosis when present, and defines the prognosis of the disease and influences survival and follow-up of these patients. Due to the cardiac involvement in KD, cardiovascular imaging plays an essential role in this setting. Imaging modalities for the diagnosis and the follow-up of patients after KD, particularly for evaluating coronary arteries include, echocardiography, CT-scan angiography (CTA), cardiac magnetic resonance (CMR) and conventional angiography. The goal is to perform a combined use of these different techniques to maximize the diagnostic accuracy for any cardiovascular complications, and to reduce the exposure to ionizing radiation. Optimal diagnostic and follow-up algorithm, for evaluating the cardiac involvement in KD are based on an expert consensus opinion, and should be updated with the recent technical advances in cardiac CT and MRI.The selection of the technique to make a functional and anatomic study of the coronary arteries in children depends on different factors such as the age, the clinical setting and the need of a therapeutic technique. In this article we review different imaging techniques available for cardiac evaluation in KD patients.*

Keywords: *Echocardiography; Cardiac magnetic resonance; CT-scan; Kawasaki disease*

1. Kawasaki Disease: Definition And Cardiac Involvement

Kawasaki disease (KD) is an acute systemic vasculitis syndrome occurring mostly in children aged 6 months-5 years. The etiology of KD is unknown, but an infectious trigger initiating an abnormal immune response in genetically predisposed children likely causes it(1,2). The diagnosis of KD is based on the presence of clinical features of persistent fever (>5 days) in combination with a polymorphous exanthema, cervical lymphadenopathy, non-purulent conjunctival injection, changes of the lips and oral cavity, and changes in extremities. Complete KD is defined as fever and ≥4 out of the 5 symptoms. Incomplete KD could be diagnosed in case ≤3 criteria are present when coronary artery aneurysms (CAA) abnormalities on echocardiography and/or laboratory abnormalities are detected(1,2). The importance of KD is that is the main cause of CAA in children, thus the main goal of treatment is prevention of the development of CAA. Of note, treatment with intravenous immunoglobulin (IVIG) before 10 days of illness has reduced the incidence of coronary artery aneurysms from 25% to 5%(1).

Cardiovascular involvement is the leading cause of long-term morbidity and mortality, thus KD is the most common cause of acquired heart disease in children in developed countries(3). The whole heart (pericardium, myocardium, endocardium including valves, and the coronary arteries) may be inflamed in acute phase of KD. So cardiovascular manifestation of acute KD can include pericarditis, myocarditis, valvular regurgitation and ventricular systolic or diastolic dysfunction(4). Coronary artery disease involvement may present with aneurysm, premature atheroma, stenosis, calcification, thrombosis, or occlusion with infarction(5). Development of coronary artery aneurysms (CAA) is the most important and widely recognized complication of KD. It confirms the diagnosis when present, and defines the prognosis of the disease and influences survival and follow-up of these patients(1,6). Vasculopathic processes in the arterial wall are well recognized (acute necrotizing arteritis, subacute/chronic vasculitis, and luminal myofibroblastic proliferation) resulting in CAA. Risk factors for CAA have been inconsistently reported but include a male gender, a young age (<1 year), an incomplete disease presentation, and an increased inflammatory state in acute

phase, IVIG resistance, and the duration of fever(7,8). Nowadays it has become clear that z-scores, diameters adjusted for basal-surface-area, may be better indication of abnormality. CAA is defined as a z-score ≥2.5, although a z-score between 2 and 2.5 can be classified as a dilation in acute phase. A small-sized CAA has a z-score of 2.5–5, a medium-sized CAA of 5–10, and a giant CAA of ≥10(9,10).

2. Cardiac Imaging In KD

Due to the cardiac involvement in KD, cardiovascular imaging plays an essential role in this setting. Although the main objective is to delineate anatomy and function of the coronary arteries, it is also important to perform an assessment of the whole heart, thus in acute phase the majority of cardiac involvement is secondary to myocarditis-pericarditis-valvulitis. Imaging modalities for the diagnosis and the follow-up of patients after KD, particularly for evaluating coronary arteries include, echocardiography, CT-scan angiography (CTA), cardiac magnetic resonance (CMR) and conventional angiography(11). The goal is to perform a combined use of these different techniques to maximize the diagnostic accuracy for any cardiovascular complications, and to reduce the exposure to ionizing radiation. The selection of the technique to make a functional and anatomic study of the coronary arteries in children depends on different factors such as the age, the clinical setting and the need of a therapeutic technique.

Echocardiography: Echocardiography is the primary imaging modality for cardiac assessment in KD patients(9,12). It is non-invasive and widely available in most centres. The development of high-frequency transducers and color Doppler imaging has allowed high-resolution two-dimensional imaging of the coronary arterial system, identification of coronary origin and direction of coronary flow. Thus it can detect well CAA of the proximal coronary arteries segments(13). It also provides rapid and easily interpretable data about myocardial function (20% of KD develop systolic dysfunction), pericardial effusion, valvular regurgitation and chambers or aortic root dilatation. Moreover it let a close and rapid follow-up in the initial stage of the disease, and can help to guide pharmacological management (diuretics, anticoagulation, repeated doses of gamma globulin…). It is important to recognize the limitations of echocardiography in the evaluation and follow-up of patients with KD. Detailed echocardiographic imaging is compromised in uncooperative and irritable patients, and sedation is frequently needed. Its capacity of detection of thrombi, calcification and coronary artery stenosis is limited. The visualization of coronary arteries becomes progressively more difficult as a child grows and body size increases and of note, distal coronary anatomy is impossible to see with detail(13).

CT and CMR: Coronary non-invasive imaging with CT or CMR must fulfil two main technical requirements: A high temporal resolution to overcome the near constant motion of the coronary arteries during the respiratory and the cardiac cycles; and a high spatial resolution to provide accurate imaging of very small vessels. Therefore, coronary artery imaging in children is frequently challenging due to small size, high heart rates, and motion artefacts from cardiac pulsation, respiration, and the patients themselves, which results in technical or procedural difficulties.

CT-scan: Coronary CT angiography is currently regarded as the diagnostic imaging method of choice for evaluating anatomy of the entire coronary artery tree(14,15). It does not need so much time to perform. It provides a detailed coronary artery morphology, it can show first-pass myocardial hypo-perfusion and delayed myocardial enhancement resulting from significant coronary artery stenosis or occlusion, and is very sensitive for visualization of coronary artery lesions such as thrombi and calcifications(15,16). The main limitations are the exposure to ionizing radiation and that the quality of imaging depends on low heart rates and lack of movement, both difficult to achieve in small children. Therefore administration of beta-blockers to reduce heart rate and sedation is usually needed. Also non-anatomic parameters such as cardiac function or tissue characterization are obtained well with CMR or echocardiography(15-17).

CMR: CMR provide high resolution 3D-imaging that lead to the evaluation of the anatomy as well as cardiac function without the risks of ionizing radiation inherent in CCT or angiography(18). CMR can detect fibrotic, infracted, or inflamed myocardium that can be present in KD, using delayed hyper-enhancement imaging techniques after intravenous gadolinium injection(19). Also stress-CMR with adenosine is very useful detecting indictable ischemia(20). However, it

remains technically challenging for coronary visualization in neonates and infants because, due to its long acquisition time and the immobility needed, it usually requires prolonged anaesthesia with risk of hypothermia in infants. Sedation is usually needed also in older children. Also, in babies, temporal and spatial resolutions are still insufficient. So only detailed proximal coronary arteries anatomy can be provided with guarantee(17,18).

Coronary CT angiography and CMR are useful in both acute phase and chronic follow-up of KD patients. Coronary artery visibility on CT and MRI tends to be compromised in young children due to the small size of the coronary arteries and very high heart rates. However recent technical improvements have lead to an increased visibility of coronary arteries with these two techniques. CTA provides greater detail of vascular structures, whereas CMR is superior for cardiovascular function and assessment of wall motion and myocardial fibrosis. So they are complementary tools in the management of KD patients.

3. Conventional Coronary Angiography

The gold standard for coronary anatomy is a conventional angiography. The main role of conventional angiography is the possibility to perform interventional procedures when need in case of coronary ischemic acute or chronic complications(1). However complications associated with selective coronary angiography are not trivial, ranging from relatively frequent minor ones including temporary electrocardiography (ECG) changes, transient bradycardia, and vascular access-related complications, to rare serious ones, such as ventricular fibrillation or cardiac tamponade(21). Besides these complications, the use of ionizing radiation and iodinated contrast agent in catheter angiography is another concern particularly in children. Furthermore, because it is a 2-dimensional projection imaging, catheter angiography lacks the 3-dimensional spatial relationship between the coronary arteries and adjacent cardiovascular structures.

4. Cardiac Imaging In Acute Phase Of KD

In the acute phase of KD (first 10-14 days of illness) the main cardiovascular findings are related to myocarditis and pericarditis in the context of an acute high inflammatory state. Although the presence of CAA confirms KD, they are present only in about 15% of patients in the acute phase, so the absence of CAA not discards the diagnosis of KD if the rest of clinical criteria are fulfilled(4,7,22). Therefore imaging techniques at this time should be focused not only in detect CAA but also myocardial systolic or diastolic dysfunction, pericardial effusion, aortic dilatation, valvular regurgitation and chambers dilatation. All these inflammatory changes are usually transient and disappear after treatment with gamma globulin.

Echocardiography is the primary imaging modality used in acute phase of the disease. It usually the only imaging technique used because it can provide data about cardiac function, cardiac inflammation (pericardial effusion or valvular regurgitation), and CAA in proximal coronary segments (15% of KD patients in acute phase)(13). The initial echocardiogram should be performed as soon as the diagnosis is suspected, but initiation of treatment should not be delayed by the timing of the study(1). Of note, it can confirm diagnosis if CAA are detected, but never discard KD if not.

Conventional angiography, CT or CMR may be used for complete initial mapping of the coronary artery abnormalities required for accurate risk stratification. Although invasive angiography, CMRI, and CTA can be of value in the acute phase of KD it seems prudent to perform these studies only in patients with severe lesions in proximal coronary arteries detected by echocardiography, in patients with a poor acoustic window or patients with high score risk for development of CAA. Of note, cardiac catheterization in the acute phase of KD has been associated with a greater incidence of adverse vascular events at the site of an arterial access vessel potentially affected by KD vasculitis, and therefore it should be reserved for interventional procedures in the rare case of an ischemic event, or when non-invasive diagnostic imaging is inconclusive.

5. Cardiac Imaging In Subacute/ Chronic Phase Of KD

In the sub acute/chronic phase of KD (>14 days) the main cardiovascular changes are sequels secondary to the high inflammatory acute state, overall CAA secondary to fibrotic changes in arterial walls. If the rare case of myocardial infarction occurred in acute state, sequels such as ventricular dysfunction and arrhythmias can develop. Also myocardial infarction can occurs more frequently in the first year after the clinical debut of KD, so a closely follow-up is warranted at this stage(2,23).

Again echocardiography is the main imaging tool used for chronic follow-up in KD, due to its high availability and its non-invasive character. For patients without CAA, echocardiography should be repeated both within 1 to 2 weeks and 4 to 6 weeks after treatment. Patients without CAA 6 months after the debut rarely develop any long-term cardiac complication, and a 1-2 yearly echocardiogram seems advisable in this setting. For patients with important and evolving coronary artery abnormalities (Z score >2.5) detected during the acute illness, more frequent echocardiography (at least twice per week) should be performed until luminal dimensions have stopped progressing to determine the risk for and presence of thrombosis. After this, a 6-month echocardiography is recommended (24,25).

Echocardiographic measurements of the coronary artery lumen become progressively less reliable as children grow and the chest wall thickens. Echocardiography is also less reliable for detection of vascular stenosis or thrombosis than for dilation. For these reasons, advanced imaging techniques, including CMR and CT-scan are playing an increasing role in the chronic follow-up of KD patients. The combined use of these two techniques provides a complete (anatomic and functional) cardiac assessment. CT-scan provides high-resolution detailed images of the whole anatomy of the whole coronary tree. It also can evaluate well coronary luminal stenosis and the presence of thrombi or coronary wall calcification. CMR provides data about cardiac function, wall motion abnormalities and the presence of myocardial scar secondary to myocardial ischemic events. Also it can show high quality images of the proximal coronary tree. For serial imaging follow-up, assessment of myocardial perfusion is generally recommended in addition to morphologic assessment of the coronary arteries. Stress myocardial perfusion imaging with both CT and MRI is being added to the cardiac imaging protocol for patients with Kawasaki disease. Also evaluation of potential aneurysmal involvement in other arterial beds can be assessed after recovery from the acute illness, and usually for patients with severe coronary artery involvement or symptoms or signs, such as the presence of a pulsatile axillary mass. Again both CMRI and CTA can make well this assessment.

The exact protocol for serial follow-up coronary imaging is not established. However, it seems adequate that studies different to echocardiography in the follow-up of KD patients should be performed based on the worst-ever z-score of CAA detected in the first 6 months of the disease. For patients with Z score < 2.5 or a low risk profile no studies different to echocardiography are needed. Maybe CMR in older children/adolescents, who not precise sedation can be recommended to detect silent and improbable myocardial scars, avoiding ionizing radiation of CT-scan. For patients with Z score > 2.5 an initial CT-scan is recommended to visualize the whole coronary anatomy, and a CMR to detect myocardial scars, in the first year of the disease. If any sequels are detected, repeated CT-scan and/or CMR at a 2-3 year interval is advisable, including ischemia-induction tests.

Once again, due to the technical advances in CT-scan and CMR, conventional angiography should be reserved for interventional procedures or when non-invasive diagnostic imaging is inconclusive.

6. CONCLUSIONS

Optimal diagnostic and follow-up algorithm, for evaluating the cardiac involvement in KD are based on an expert consensus opinion, and should be updated with the recent technical advances in cardiac CT and MRI. While echocardiography has remained the main tool in cardiac imaging in children with KD, it is reasonable to obtain advanced imaging studies such as computed tomographic angiography (CTA), cardiac magnetic resonance imaging (CMRI), or invasive angiography on high risk patients or patients where echocardiography does not reveal adequate information. Cardiac MRI and CT angiography have complemented echocardiography in these children and have replaced the more invasive and traditional procedures of cardiac catheterization.

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Citation: *Moises Rodriguez-Gonzalez, MD, Ana Castellano-Martinez, MD. Cardiac Imaging in Kawasaki Disease. ARC Journal of Radiology and Medical Imaging. 2018; 3(1): 7-11.*

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