

# Kawasaki Disease A Vasculitis of Infancy with Vascular Coronary Implications in Adulthood

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## ABSTRACT

Kawasaki disease is a vasculitis of the medium sized arteries, widely spread in developed countries and of unknown etiology. The diagnosis is clinical and is based on the criteria established by the American Heart Association. The most redoubtable cardiovascular finding of the disease is the coronary aneurysm; its incidence can be drastically reduced by a timely first line therapy (intravenous immunoglobulin and aspirin at antiinflammatory dosage). The resistant cases are treated with a second dose of IVIG or, secondarily, with infliximab, methylprednisolone, cyclosporine or abciximab.

Several studies have demonstrated the association between childhood Kawasaki disease and adulthood atherosclerosis; moreover is attested that the intimal thickening of the left main and left anterior descending coronary artery is a predictor of subclinical atherosclerosis. On this basis, we conducted an observational cross-sectional case control double blind study about the

assessment of coronary artery intimal thickening in patients with previous diagnosis of Kawasaki disease by using high resolution transthoracic echocardiography. We enrolled 31 cases and 26 controls with no any significant difference in subjective and laboratory parameters. We detected significant higher thickening values adjusted for BSA in cases than healthy controls, confirming the association investigated and Demonstrating that the coronary intimal impairment was independent from the cardiovascular risk class assigned in the acute phase. Concluding, a long term follow up should be performed in all subjects with a history positive for Kawasaki disease. At the same way the anamnesis of possible Kawasaki disease during infancy should be ruled in adult patients suffering of early coronary stenosis or ectasia.

**KEYWORDS:** Kawasaki disease; Coronary aneurysms; Intimal thickening; infancy; Atherosclerosis; Adults

## BACKGROUND

Kawasaki disease (KD) is a common self-limited acute vasculitis which typically occurs in children younger than five years and affects the medium sized arteries, with a predilection for the coronary arteries. It was firstly described in 1967 by Tomisaku Kawasaki a clinician who, observing 50 Japanese cases, defined the disease as a “Infantile acute febrile mucocutaneous lymph node syndrome with specific desquamation of fingers and toes”. Because in many cases the disease was self-limiting, initially it was thought that it was benign. The meeting of Kawasaki T. with other pediatrician who had experienced some sudden death cases led to discover that in some instances the syndrome could causes the development of coronary aneurysms. The subsequent introduction of two-dimensional echocardiography surely changed the management and the prognosis of the KD [1].

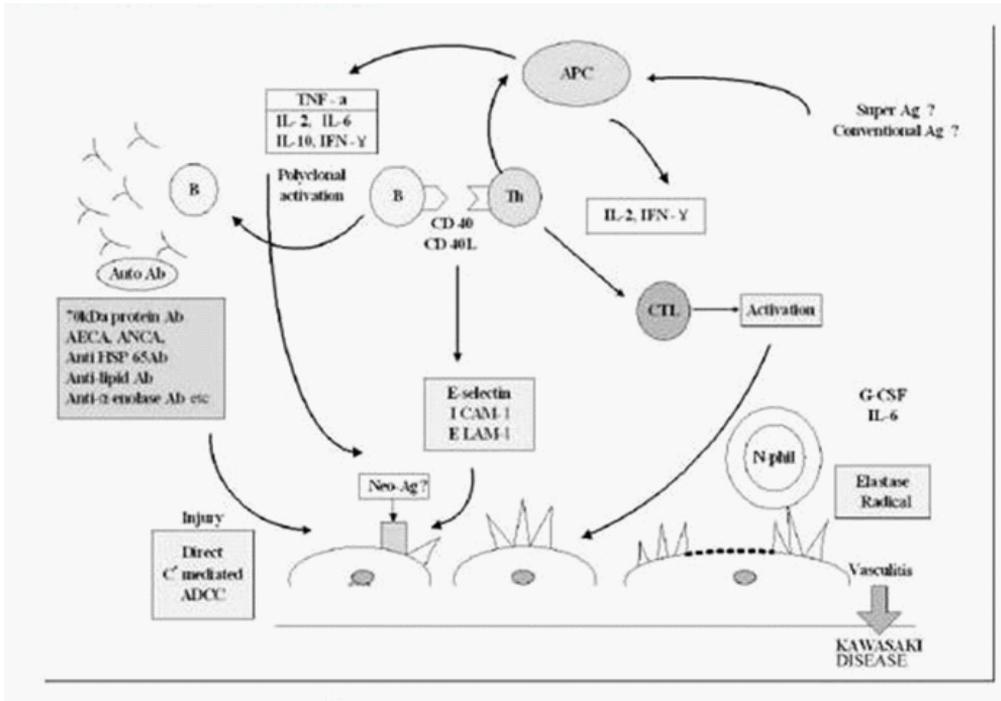
## Epidemiology

Nowadays the KD is the most common acquired cardiovascular disease of children in developed countries, as well as the second most common multisystem vasculitis of infancy and childhood in countries as United States. Though the disease has been reported in all racial and ethnic groups, there are significant differences in epidemiological distribution, with a heightened incidence in Japan and in Asian descent (inside and outside Asia). The epidemiological surveys observes a worldwide male predominance, with a male to female ratio between 1,5:1 to 2:1, and a marked seasonality of the disease, with a heightened incidence in summer in Asian countries and winter and spring peaks in temperate climates. It is universally known that the incidence of the syndrome worldwide is spreading, probably also consequently to a better knowledge of the disease [2,3].

## Etiology

In spite of the numerous attempts to identify an etiological agent, the cause of Kawasaki disease remains still unknown. It has been hypothesized that KD results from the exposure of

genetically predisposed individuals to environmental triggers (Figure 1). The involvement of genetic factors is confirmed by many evidences: the heightened incidence in East Asian children, the higher risk within families and the association of the syndrome with several single nucleotide polymorphisms [2,4].



**Figure 1:** Patterns of the pathogenesis of KD [12].

ADCC: Anti-endothelial antibody-Dependent Cell-mediated Cytotoxicity; AECA: Anti-Endothelial Cell Antibodies; ANCA: Anti-Neutrophil Cytoplasmic Antibodies; APC: Antigen-Presenting Cell; CD40L: CD40 ligand; CTL: Cytolytic T Lymphocyte; ELAM-1: Endothelial-Leukocyte Adhesion Molecule-1; G-CSF: Granulocyte Colony Stimulating Factor; ICAM 1: Intercellular Adhesion Molecule-1; IFN: Interferon; HSP: Heat Shock Protein; TNF: Tumor Necrosis Factor.

The genes related to innate and acquired immunity or to vascular remodeling have been studied by the genome-wide linkage and the genome-wide association studies. It has been identified a single nucleotide polymorphism (SNP) within the CD40 ligand gene, which encodes for a protein expressed in antigen- presenting cells with the function of transducing signals related to cell activation and development. The over-expression of the ligand has been observed during the acute phase and in the coronary artery disease of KD Japanese patients. Another prominent discovery was the SNP of the inositol 1,4,5-triphosphate (IP3) kinase C (ITPKC) gene, a second messenger molecule involved in the Ca<sup>2+</sup>/NFAT pathway which is a T-cell activity modulator and predisposes both Japanese and American subjects to KD and to the subsequent coronary

disease. Recently it has been discovered an association of a SNP within the Fc gamma receptor gene cluster on chromosome 1 with the susceptibility for KD. In particular, the association was seen on rs1801274 on the Fc fragment of IgG, a low affinity Ila receptor (FCGR2A) gene, whose protein stimulates the transducing activation signal into the cells where expressed, as monocytes, dendritic cells, neutrophils and macrophages. Several other nucleotide polymorphisms have been observed, even though larger studies should be performed. The association between HLA alleles and KD is controversial; an association with HLA-DQB2 and HLA-DOB is suspected. Many authors have questioned about the overlapping of genetic components observed in KD with other inflammatory and autoimmunity disorders. On this regard, the SNP of FCGR2A described for KD is associated with an increased risk of ulcerative colitis and a decreased risk of systemic lupus erythematosus.

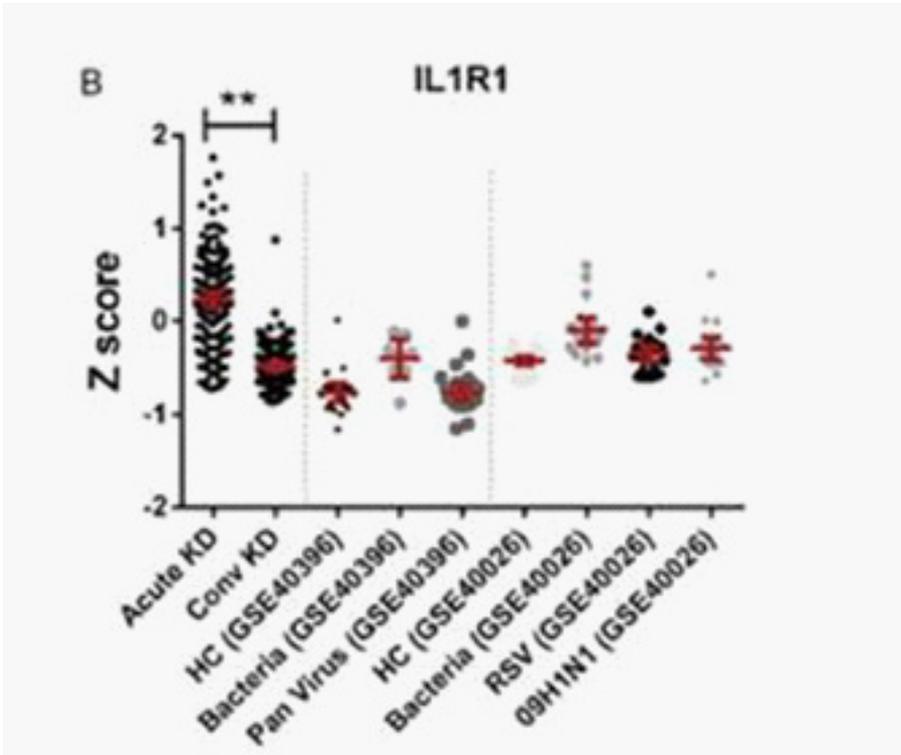
Then the SNP of a segment of CD40 has been associated with KD as well as with multiple sclerosis, systemic lupus erythematosus and rheumatoid arthritis. These data suggest that KD shares part of the gene network with other inflammatory disorders [5-9].

The infectious trigger of KD is suggested by the seasonality of cases, the self limited nature of the acute illness and the nationwide epidemics. It has been noticed that more than 33% of KD patients have at least one concomitant infection at the time of diagnosis. Moreover, there has been observed a high concentration of IgA plasma cells in the respiratory tract during the acute phase, suggesting a respiratory portal of entry of the etiological agent. Then, it is possible that, among environmental factors, a bacterial superantigenic toxin could be involved. This is supported by the selective expansion of V $\beta$ 2 and V $\beta$ 8 T-cell receptor families in the acute phase of the disease [10-12].

## Immunopathogenesis

The acute phase of KD is characterized by a swelling of endothelial cells, an edema of subendothelial and media layer and by the dissociation of the smooth muscle cells. The vessel wall is usually infiltrated by neutrophils, CD8<sup>+</sup> T cells and IgA secreting plasma cells. In the subacute phase the internal elastic lamina could dissociate and the fibroblastic proliferation could occur [4]. During the acute and the convalescent phase many immunological events are observed. Recently, it has been conducted a study with the aim of identifying differentially abundant transcripts in KD patients in comparison to patients with confirmed bacterial or viral infection and with healthy controls. It revealed that the IL1 signaling pathway and the innate immunity have a prominent role in the acute phase (Figure 2). Then, a decreased transcript abundance of CYP26b1, a negative regulator of retinoic acid signaling, is associated with forms complicated with coronary artery aneurysms. These results suggest new opportunities of treatment for KD, such as agents that block the IL-1 signaling pathway and agents that stimulate the retinoic acid signaling pathway toward T cell regulation. Moreover, a different response to the Intravenous Immunoglobulin (IVIG) corresponds to a different cell activation: the IVIG responders have a predominant recruitment of T cell and Natural Killer, otherwise the IVIG non responders have an

increase in neutrophils infiltration. The response to the treatment is so conditioned by the type of the immune response [13].



**Figure 2:** Interleukin 1 signalling pathway in KD and in other disease [13].

The figure shows increased IL1R1 different expression in acute vs convalescent KD compared with other viral and bacterial infections.

## CLINICAL FEATURES

Presently, KD continues to be a disease with several pitfalls. The main difficulties for clinicians are how to perform a timely diagnosis, how to prevent cardiovascular complications, and how to treat refractory forms [14,15]. In the absence of a specific diagnostic test, diagnosis is based on clinical criteria established by the Japanese Ministry of Health and then adopted by the American Heart Association (AHA). The diagnosis of Kawasaki disease indeed requires the presence of fever lasting at least five days without any other explanation combined with at least four of the five following criteria: bilateral bulbar conjunctival injection; oral mucous membrane changes (injected or fissured lips, injected pharynx, or strawberry tongue); peripheral extremity changes (erythema of palms or soles, edema of hands or feet- acute phase-, and periungueal desquamation -convalescent phase-); polymorphous rash and cervical lymphadenopathy (at least one lymph node > 1,5 cm in diameter). The typical form consists of four phases: acute, subacute, convalescent and chronic phase. The first phase is characterized by the clinical signs described

above, sometimes associated with cardiac manifestations; it commonly lasts from 1 to 2 weeks. In the second phase the fever usually resolves, even though the risk of fatal heart involvement rises and in the convalescent phase the cessation of symptoms and the normalization of laboratory findings occur. The final chronic phase describes follow up management due to coronary artery involvement [16,17].

In several cases KD begins with an uncommon clinical feature. These forms are known as “atypical” and “incomplete” forms and are more commonly observed in children younger than 6 months and older than five years. A child is said to have the “incomplete” KD when the fever (of duration > 7 days) is associated with less than four clinical features and coronary complication or in the presence in an infant younger than 6 months of fever that lasts more than 5 days, systemic signs of inflammation and coronary artery involvement. On the other hand the “atypical” KD is defined by the association of fever with atypical manifestations (such as gallbladder hydrops or nephritis) and cardiac findings [16,14]. The wide spectrum of manifestations of KD is summarized in Table 1. Considering the heterogeneous onset of the KD, the differential diagnosis with other infectious and no-infectious febrile diseases is required. It includes EBV, adenovirus, echovirus, rocky Mountain spotted fever, leptospirosis, scarlet fever and shock syndrome, among infectious diseases, and idiopathic juvenile arthritis, polyarteritis nodosa, juvenile mercury poisoning and adverse drug reactions, among others [2,18-20].

**Table 1: Manifestations of KD.**

<b>Cardiological:</b> coronary artery disease, endocarditis, mitral insufficiency, tricuspid insufficiency, aortic insufficiency, aortic bulb dilatation, cardiac insufficiency, cardiac shock, arrhythmia
<b>Vascular:</b> Reynaud phenomenon, peripheral gangrene
<b>Articular:</b> Arthritis, articular pain
<b>Nervous:</b> Irritability, aseptic meningitis, neurosensorial hearing loss, unilateral facial nerve palsy
<b>Gastrointestinal:</b> Diarrhoea, vomiting, acute abdomen, hepatic disease, gall bladder hydrops
<b>Urinary:</b> Sterile pyuria, urethritis, hydrocele.
<b>Cutaneous:</b> Beau lines, erythema and induration at the site of previous vaccination with Bacille Calmette-Gurin
<b>Respiratory:</b> Cough, rhinitis, lungs nodular lesions

The clinical features of KD involve several organs and apparatus. The table shows the possible manifestations for each organ and apparatus.

Even though the diagnostic criteria used in Europe are the AHA criteria cited above, it exists another set of diagnostic criteria established by the Japanese Kawasaki Disease Research Committee in 2004 and mainly used in Japan. According to these criteria, the diagnosis could be done if five of the following six criteria are respected: fever persisting more than 5 days; bilateral conjunctival congestion; changes of lips and oral cavity; polymorphous exanthema; changes of peripheral extremities; acute non-purulent cervical lymphadenopathy. Indeed, the main difference with the AHA criteria is that the presence of fever for at least five days isn't an essential prerequisite for the diagnosis [16,21].

# LABORATORY FINDINGS

Even if non-specific, there are certain laboratory findings recurrent in KD. In the acute phase have been observed leukocytosis, elevated erythrocyte sedimentation rate and C-reactive protein, moderate elevation of serum transaminases and hypoalbuminemia, sometimes associated with sterile pyuria, depressed plasma cholesterol and high-density lipoprotein. Otherwise the subacute phase is characterized by thrombocytosis (sometimes exceeding  $1.000.000/mm^3$ ) (10). The laboratory findings observed in KD are summarized in Table 2.

**Table 2:** Laboratory findings of KD.

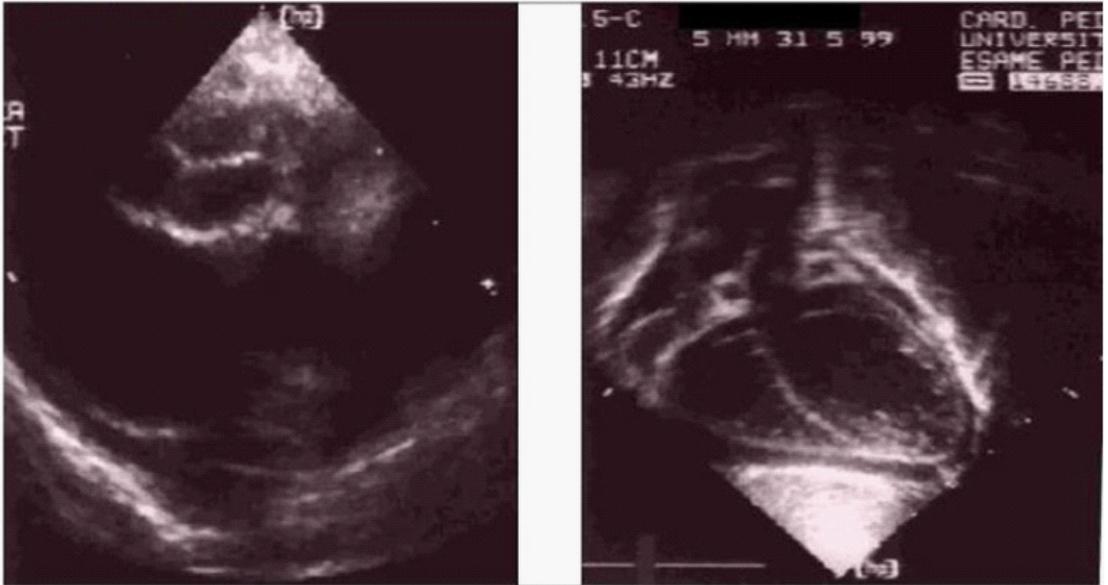
Normochromic normocytic Anaemia for age
Leukocytosis (white cell count > $15.000/mm^3$ )
Erythrocyte sedimentation rate > 40 mm/h
Increase of C-reactive protein
Elevated aminotrasferase
Albumin < 3 g/dl
Piastrinosis (subacute phase)

## Cardiovascular findings

The cardiovascular manifestations prevail in the acute phase of the disease and may involve pericardium, myocardium, endocardium, valves and coronary arteries. Up to 25% of untreated children will develop permanent damage to the coronary arteries with aneurysm formation. The incidences of aneurysms reduces to 3-5% if the children are treated with the first line medication (intravenous immunoglobulin). The transthoracic echocardiography with the study of proximal coronary arteries permits the measurement of the internal diameter of the right and left proximal descending arteries and may show ectasia, defined by a z score normalized for body surface area (BSA) if the dilatation is > of 2,5 or by the presence of a segmental aneurysm [2,16,22,23]. The AHA classifies the aneurysms as small (5 cm diameter), medium (5-8 mm diameter) and giant (8 mm diameter). The risk factors of coronary artery aneurysm are: higher values of platelet count, age < 6 months, hospital admission > 6 days, low serum albumin, longer duration of fever and incomplete KD [24]. The coronary abnormalities (Figure 3) occur more frequently during the subacute phase, even though many authors have signaled cases developed few days after the onset of fever [14]. For this reason, the AHA guidelines establish that the echocardiography should be performed at the time of diagnosis and then at 2 weeks and at 6-8 weeks of illness. The long term echocardiography follow up depends on the risk stratification (Table 3). At level I and at level II children should be evaluated at about five year intervals. Otherwise the III level of risk entails an annual cardiology follow up. The IV level and the V level of risk require a twice per year follow up and invasive testing if necessary [25].

**Table 3:** Risk stratification of myocardial infarction according to AHA.

Risk Level	Coronary disease description
I	No coronary arteries changes
II	Transient coronary ectasia (resolves within 8 weeks)
III	One small-medium aneurysm in one major coronary artery
IV	>1 Large or giant coronary artery aneurysm or multiple or complex aneurysms in the same coronary artery without obstruction
V	Coronary artery obstruction



**Figure 3:** Giant Left coronary aneurysm. Dilated right coronary with thicked intimal wall. Pericardial Effusion.

## TREATMENT

In the acute phase, the aim of the treatment is to reduce the inflammation in the coronary artery wall and to prevent coronary thrombosis whereas the long-term therapy, especially in patients with coronary ectasias or aneurysms, is to prevent myocardial damage.

In the acute phase, the current standard of therapy is a single dose of 2 gr/kg intravenous immunoglobulin (IVIG) infused over 10-12 hours within ten days of fever onset. It is usually associated with aspirin at the anti-inflammatory dosage of 30-50 mg/k/d spread out over 4 doses until the child has been afebrile for 48-72 hours. Then the aspirin is continued at a single daily dose of 3-5 mg/k/d for 4-6 weeks or more if coronary artery abnormalities fail to regress by this time. The beginning dosage of aspirin has been recently lowered from 80-100 mg/k/d to 30-50 mg/k/d because of the risks connected to the high dose aspirin administration, as

gastrointestinal bleeding, Reye's syndrome and sensorineural hearing loss [16]. According to this standard therapy, 80-90% of treated patients show a clinical and biochemical remission; in the remaining percentage of patients a persistent fever or a recurrent fever at least after 36 hours after the infusion of the IVIG represents a sign of unresponsiveness to IVIG which is the major risk factor for the development of coronary artery lesions [14,26]. Kobayashi [26], Egami [27] and Sano [28] proposed three different scoring systems in order to identify the patients at high risk of unresponsiveness to therapy with IVIG. The treatment of IVIG resistant cases includes a second dose of IVIG at the same dosage of the first one and, in case of persistence, infliximab (5 mg/kg/iv), methylprednisolone (30 mg/kg/d for 3 days), cyclosporine or abciximab amongst others. Leonardi S et al. [14] had suggested an association of intravenous methylprednisolone and IVIG during an early phase of the disease if the score indexes are predictive of a high risk form, to prevent an IVIG resistance. This theory has been confirmed by recent Japanese studies which have shown that glucocorticoids when administered with IVIG had a beneficial effect in terms of earlier resolution of fever and normalization of raised inflammatory markers [16,29,30].

The aneurysm management in the acute phase depends on the severity of the coronary artery involvement. In patients with symptomatic myocardial ischaemia or laboratory findings suggestive of it, or in case of severely stenotic lesions, percutaneous coronary intervention procedures should be performed. They consist on stent implantation, rotational ablation, balloon angioplasty and intracoronary thrombolysis [2,31,32]. Anyway, if coronary artery abnormalities fail to regress by 6-8 weeks from the onset, long term pharmacological antiaggregant/anticoagulant therapy is implicated. The choose of the drug depends on the severity of the coronary disease. Asymptomatic patients with a low- moderate grade coronary disease, require a treatment with aspirin at the dosage of 3-5 mg/kg/die. If high grade coronary disease, the association of aspirin with dipyridamole or clopidogrel at the dosage respectively of 2-6 mg/kg/d in 3 doses and 1 mg/kg/d is suggested. Patients with rapidly evolving aneurysms are treated with aspirin associated with low molecular weight heparin (3 mg/kg/d in two administration for ages < 12 months, 2 mg/kg/d in two administration for older ages). Giant aneurysms should be treated with the same treatment of the rapidly evolving form or with the association of aspirin and warfarin (0.1 mg/kg/d). The use of warfarin requires the periodic dosage of serum INR, that must range from 2 to 2,5 [33].

Finally, official recommendations state that active immunizations should be delayed by 11 months in children who have received treatment with IVIG [2].

## **LONG TERM FOLLOW UP: OUR EXPERIENCE**

### **Background**

While the acute inflammatory damage to coronary arteries in the acute phase of KD has been well described, controversial remains the vascular health late after KD [34,35]. The occurrence of

myocardial infarction has been reported both in KD patients, many years after the development of coronary artery aneurysms, and in young adults with “missed” KD diagnosis in childhood. A recent murine study have suggested a pathophysiologic link between coronary arteritis and acceleration of atherosclerosis [36]. Several studies have demonstrated the development of abnormalities in architecture of coronary arteries in regressed coronary aneurysms, detected by intravascular ultrasound and anatomic-pathological analysis [37-41]. Otherwise there are few evidences about coronary artery assessment in individuals whose echocardiograms showed no evidences of structural damage at diagnosis. Attested that the intimal thickening of the left main and left anterior descending coronary artery is a predictor of subclinical atherosclerosis, we proposed to study that thickening in patients with a previous diagnosis of KD several years after the acute event [42,43].

## Our experience

We conducted an observational cross-sectional case control double blind study about the assessment of coronary artery intimal thickening in patients with previous diagnosis of Kawasaki disease by using high resolution transthoracic echocardiography. The case group was composed by 31 patients with a previous diagnosis of KD (according to the criteria of the AHA), hospitalized in our Pediatric Department of the University of Catania (Italy) between January 1990 and December 2000. Five of the case patients were omitted because current smokers. The 26 controls were recruited among voluntary healthy students. The average age of cases at the time of the enrollment was  $13,3 \pm 7.4$ , ranging from 4 to 27 years. The time from the beginning of the disease ranged from 3 to 22 years. Of each case subject, the following features at diagnosis were investigated: the clinical form, the ECG, the cardiac manifestations, the risk class, the therapy and the age at diagnosis (Table 4). Both in cases and controls were measured: the BMI, the lipid profile, the C-reactive proteins, the platelet count and the blood pressure. We performed Electrocardiogram and 2D Echocardiography in all patients, assessing the measurement of thickening, inner diameter and outer diameter of coronary arteries and examining the proximal portion of the left main coronary artery just above the aortic valve with parasternal short axis view. The values of coronary thickening were adjusted for Body Surface Area (BSA) (Table 5). Attested that there was not found any significant difference in subjective and laboratory parameters between patients and healthy controls, we detected significant higher thickening values adjusted for BSA in cases than healthy controls. Moreover we noticed significant difference in thickening values between controls and respectively patients belonging to risk class 1 and class 2-3-4- group, without statistically significant difference between classes (Table 6). Concluding, our study showed that the significant thickening of coronary intimal wall of cases was not related to the severity of the cardiovascular damage during the acute phase (Figure 4 and Figure 5) [44].

**Table 4:** Features of cases at diagnosis.

Gender	Clinical form	ECG	Cardiac manifestations	Risk class	Therapy	Age at diagnosis
M:18(69.2%)	T: 14 (53.8%)	N: 12 (46.2%)	NCI: 14 (54%)	I: (20 (76.9%)	ASA +IVIG 20 (76.9%)	< 6 ms: 2 (7.7%)
F:8 (30.8)	1: 9 (34.6%)	SST:9 (34.6%)	TAC: 3 (11.5%)	II. 3 (11.5%)	ASA 3 (11.5%)	6ms- 5 ys: 21 (80.8)
	A: 3 (11.5%)	PRBBB: 3 (11.5%)	PAC: 3 (11.5%)	III. 2(77%)	IVIG 2 (7.7%)	> 5ys:3 (11.5%)
		NSDVR: 2 (7.7%)	PE: 3 (11.5%)	IV: 1 (3.9%)	No Therapy (3.9%)	
			MR: 3 (11.5%)			

M: Male; F: Female; T: Typical; I: Incomplete; A: Atypical; N: Normal; SST Slight Sinus Tachycardia; PRBB: Partial Right Bundle branch Block; NSDVR: Non Specific Disorders of Ventricular Repolarization; NCI: No Cardiac Impairment; TAC: Transient Anomalies of Coronaries; PAC: Persistent Anomalies of Coronaries; PE: Pericardial Effusion; MR : Mitral Regulation.

**Table 5:** Thickening and thickening adjusted for BSA in cases and healthy controls.

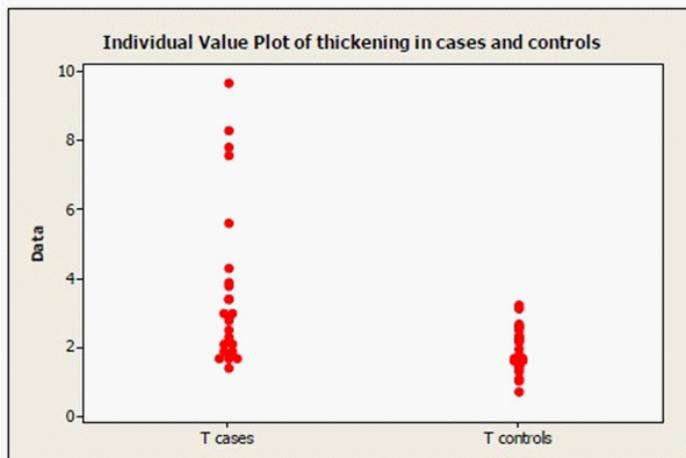
Parameter	Cases	Controls	P value
Thickening (mm)	3.5 ± 2.2	1.9 ± 0.6	< 0.01
Thickening adjusted for BSA (MM)	5.3 ± 4.4	2.7 ± 1.2	<0.01

**Table 6:** Thickening and thickening adjusted for BSA in controls, patients belonging to risk class 1 and patients belonging to risk class 2-3-4 group.

Category	Thickening (mm)	Thickening adjusted for BSA (mm)
A (controls)	1.9 ± 0.6	2.7 ± 1.2
B (Risk class 1)	3.0 ± 1.7	4.5 ± 3.7
C (Risk class 2-3-4)	5.3 ± 3.1	7.9 ± 5.8

Thickening: A versus B; p < 0.01; A versus C; p < 0.01, B versus C; NS

Thickening adjusted for BSA: A versus B; p < 0.05; A versus C; p < 0.05; B versus C: NS



**Figure 4:** Individual value plot of thickening in cases and controls.



**Figure 5:** Abnormal left main intimal thickening.

## DISCUSSION

The intimal thickening of coronary arteries has been previously observed both by intravascular ultrasound and by anatomopathological studies.

In 1994 Sigmura et al. [37] reported in KD patients examined 9 years after the acute phase an intimal thickening at the site of persistent or regressed coronary aneurism and at segments near, using intravascular ultrasound. The same phenomenon was observed some years later by Suzuki [38] et al. In 2009 Mitani et al. [39], using virtual histological-intravascular ultrasound, found many plaque areas in coronary arteries later after KD, due to fibrosis, dense calcium areas and necrotic core.

The anatomo-pathological studies clarify the pathogenesis of vascular damage. Takahashi et al. [40] detected in six autopsy cases older than 15 years with previous coronary arterial lesions caused by arteritis in childhood a “new intimal thickening” in addition to the preexisting intimal thickening caused by the acute phase of the disease. Suzuki et al. [41] observed in all 7 subjects died several years after KD and examined at autopsy, an active remodeling of the previous aneurysms with intimal proliferation and neoangiogenesis. Afterwards, the intimal thickening detectable in KD patients seems to be caused by myointimal proliferation, intimal neoangiogenesis, disruption of internal elastic laminal and medial smooth muscle cell necrosis with replacement by fibrosis and calcification.

## CONCLUSIONS

Nowadays a growing number of adult patients with cardiovascular sequels after KD gets to the attention of adult cardiologists [45]. Attested that the cardiovascular consequence and symptoms of KD often appear two decades after the onset of the acute disease, it is necessary to establish the correct management of the adults with antecedent KD. Firstly, a past history of complicated and uncomplicated KD must be investigated by all adult internists and cardiologist. Then KD patients should be tested by the dosage of lipid profile, high sensitivity C-reactive protein level, ECG, two dimensional transthoracic echocardiogram and stress echocardiogram every 3-5 years. Also cardiac MRI may be useful in the follow up evaluation of those patients [25,46]. According to our experience we can state that the measurement of left proximal coronary intimal thickening by high-resolution transthoracic 2D Echocardiography should be added in the follow up protocol of Kawasaki disease. It can prematurely identify the atherosclerotic disease, with the advantage of uninvassiveness and reproducibility.

## FUTURE PERSPECTIVES

The acceleration of the cardiovascular risk later after KD is related to structural alteration of coronary arteries, as demonstrated above, but also to other vessels' abnormalities. Indeed, arterial stiffening (due to the smooth muscle disease), endothelium dysfunction (in terms of delayed vasodilatation in response to local stimulus) and reduced myocardial flow reserve (in terms of diffuse reduction of dilatation capacity of the microcirculation) have been reported with both coronary and systemic arteries involmment [34].

Moreover, there is increasing evidence that a low vascular inflammation persists in the long term in KD subjects. Many authors have questioned about the way to prevent the development of progressive vascular damage. Whereas in certain conditions the number of circulating endothelial cells (CECs) in the peripheral blood can reflect the severity of the endothelial damage [46,47], some authors hypothesized that it may be the cause of the progressive systemic arterial dysfunction in patients previously affected by KD. Mostafavi N et al. [48] demonstrated a higher number of CECs in KD case group than in controls, late after an acute phase of uncomplicated KD (four to ten years later). This finding could suggest that in these patients prolonged administration of vascular anti-inflammatory agents may be effective for preventing atherosclerosis in the subsequent years.

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