

# Kawasaki Disease in a Tertiary Pediatric Referral Center in Athens, Greece and Review of the Literature

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## 1. Introduction

Kawasaki disease (KD), an acute febrile mucotaneous lymph node syndrome, was initially described as a distinct clinical entity in 1967 by the Japanese physician, Dr Tomisaku Kawasaki (Kawasaki et al., 1974). Today the disease is recognized as an acute self - limited vasculitis of unknown etiology that predominantly affects young children of all racial and ethnic groups (Shulman et al., 1987). It is characterised by prolonged fever unresponsive to antibiotics, a polymorphous skin rash, erythema of the oral mucosa, lips and tongue, erythema of the palms and soles, bilateral conjunctival injection and cervical lymphadenopathy. This disease has become the leading cause of acquired heart disease among children in the developed world, with coronary artery aneurysms occurring in up to 25% of untreated cases (Newburger & Fulton, 2004).

## 2. Epidemiology

Approximately 85% of children with KD are aged less than five years, with a relatively higher incidence reported for boys (Chang, 2002). Patients either younger than three months or older than five years are scarcely encountered and are regarded to be at a higher cardiovascular risk (Burns et al., 1986; Stockheim et al., 2000). Occurrence beyond late childhood is extremely rare. Less than 100 cases of adult KD have actually been reported in the world literature since the recognition of this illness, according to a 2010 case series and review of the disease in adults (Gomard - Mennesson et al., 2010; Wolff et al., 2007). In fact, many of the reported cases in adults have been misdiagnosed as KD, while the correct diagnosis was toxic shock syndrome ( Meissner & Leung 1995; Shulman et al., 1995).

The epidemiology of KD is best documented in Japan, where regular nationwide epidemiological surveys are being conducted every two years since 1970. Based on the recent 20th survey, the number of patients with KD are continuously increasing, with an average annual incidence rate in 2007 and 2008 that reached 217/ 100.000 children younger

than five years of age, while the same value was 184.6/100.000 for the years 2005 and 2006 (Nakamura et al., 2010, 2008). Over the past years, incidence figures have also been reported based on surveys upon hospital admission from Korea, Taiwan, the United States of America and the United Kingdom, enabling comparisons to be made. The highest incidence rate of KD per 100.000 children less than five years of age is recorded in Japan. Korea and Taiwan hold the second and third place respectively (Huang et al., 2009; Park et al., 2011). The United Kingdom and the United States are credited with a significantly lower annual incidence, which however, shows an increasing tendency over the past years (Harnden et al., 2002; Holman et al., 2010).

A study performed from 1996 through 2001, showed that the annual incidence rate for KD among children younger than five years of age was 45.2 in Hawaii, the highest figure in the United States (Holman et al., 2005). Interestingly, the study showed that Japanese children in Hawaii were more likely to develop Kawasaki disease than children of other races in the same state or even children living in Japan. It is thus suggested that the incidence rate is higher in children either living in East Asia or being of Asian ancestry and living in other parts of the world. The overall prevalence in the United States is the highest among Asian and Pacific Islanders, intermediate in non-Hispanic African-Americans and the lowest for Caucasians (Holman et al., 2010a, 2010b).

Other than the racial variations in the different geographical areas, a seasonal parameter in the distribution of KD cases also seems to exist. In most countries that hold records of KD occurrence, the greatest frequency is noted during winter months. In Japan, the disease shows a bimodal seasonality, that peaks once in January and secondly in June and July (Burns et al., 2005). Moreover, a bimodal pattern of occurrence is reported in Korea (Park et al., 2011). In Taiwan, recent studies have shown that KD is noted most frequently in the summer and least frequently in the winter (Huang et al., 2009). It is therefore noticed that although the period may not always be the same, seasonal clustering of the disease does take place. Such seasonality and temporal occurrence suggest that infectious agents or other environmental factors that are yet unknown, might trigger the onset of the disease.

The standardized mortality ratio associated with KD is 1,14 (Nakamura et al., 2008). There is a slightly increased mortality ratio in boys with the disease, which is mainly recorded during the acute phase and returns to baseline thereafter. This likely reflects the fact that cardiac and coronary artery abnormalities occur more frequently in boys than in girls and that most deaths related to KD are due to acute phase coronary disease or cardiac complications. In a study conducted in Japan, researchers have concluded that the mortality rate among males with cardiac lesions due to KD appeared to be higher than in the general population. Meanwhile, the mortality for girls with cardiac sequelae and for both male and female patients without sequelae, was not elevated (Nakamura et al., 2008).

In a retrospective study we conducted in "P & A Kyriakou" Children's Hospital, a tertiary pediatric referral center in Athens, Greece, we retrieved thirty-four cases of KD within a period of 16 years (1989-2005). The age upon diagnosis was between 2 months to 11 years (average: 2.9 years) and there was no significant gender preference (18 girls versus 16 boys). The duration of hospitalization varied from 5 to 29 days depending on the severity of associated symptoms. Thirty two children were Greek and 2 were of Albanian origin. In regards to seasonality, 58.8% of the cases occurred between November and March of any given year as depicted in figure 1.

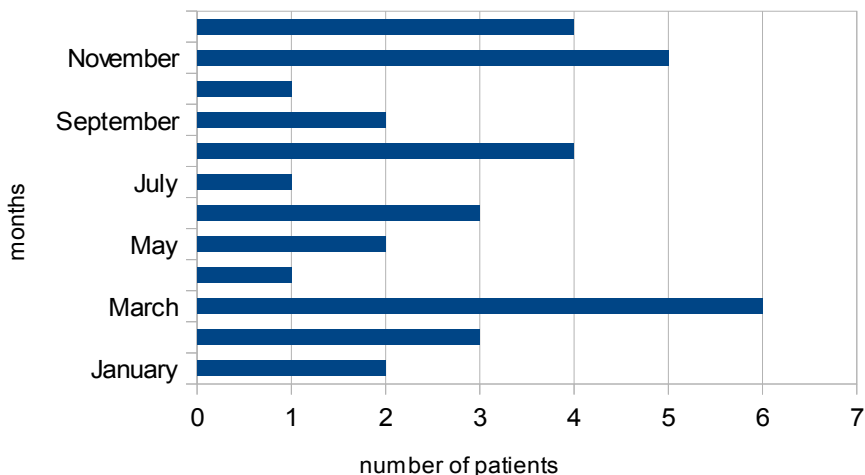


Fig. 1. Monthly distribution of the 34 cases hospitalized for Kawasaki disease in "P & A Kyriakou" Children's Hospital in Athens, Greece between the years 1989 and 2005

### 3. Aetiology

The cause of KD remains unknown. Most investigators suspect the existence of an infectious agent or the response to one or more pathogens to be responsible for the development of the disease. Evidence supporting this hypothesis includes the following:

- Seasonal clustering of KD during the winter months in most geographical areas (Burns et al, 2005).
- Geographical distribution of recorded periodic epidemics (Kao et al., 2008; Yanagawa et al., 1999).
- The fact that the disease occurs most often among toddlers, with only rare cases of infants younger than three years of age, which suggests the involvement of transplacental antibodies. Maternal immunoglobulin G may offer some protection to young infants and this protection diminishes as levels of maternal antibodies decrease (Burns & Glode, 2004).
- The 3-5 % of recurrency among cases in Japan, that may suggest either an aberrant immune response in this particular group of patients or the existence of more than one infectious agents responsible for the disease (Hirata et al., 2001).
- The clinical presentation of the disease with fever, cervical lymphadenitis, exanthema and conjunctivitis that resembles other infectious diseases such as scarlet fever and toxic shock syndrome (TSS).

While the infectious agent hypothesis remains plausible, research on associating KD with a specific pathogen has been yet fruitless. A wide variety of microbiological and molecular methods have been employed in order to isolate pathogens from body fluids and/or detect

agent - specific nucleic acids retrospectively, however with limited results (Kawasaki et al., 1974; Melish et al., 1976; Rowley et al., 1994). Although there have been numerous reports suggesting the involvement of infectious agents such as Parvovirus B19, Bocavirus, Cytomegalovirus or other viruses, *Propionibacterium acnes*, Rickettsiae, and Yersinia, none of these agents have been seen consistently isolated in children with KD (Catalano-Pons et al., 2007; Esper et al., 2005; Wang et al., 2004). Among the 34 cases of children hospitalized with KD in our study, some were examined for a variety of infectious agents as presented in table 1. Most of the children were tested negative for recent exposure to the tested infectious agents. Nevertheless, the small number of subjects tested and the lack of a control population precludes any definitive conclusions.

	Children tested	% IgM (+)	% IgM (-)	% IgG (+)	% IgG (-)
EBV	16	-	100	12,5	87,5
Parvo B19	10	-	100	30	70
CMV	14	-	100	21,4	78,6
Coxsackie - Virus	10	10	90	10	90
	1	-	100	10	90
	1	10	90	-	100
ECHO - Virus	13	23	77	-	-

Table 1. Microbiological findings among the 34 cases of Kawasaki disease identified in "P & A Kyriakou" Children's Hospital, Second Department of Pediatrics, University of Athens, Greece during the period 1989-2005

Due to the aforementioned clinical resemblance of KD with scarlet fever and TSS, it was suggested that superantigens, especially toxic shock syndrome toxin - 1 (TSST-1) and group A streptococcal exotoxins A, B and C (SPEA, SPEB, SPEC) may be involved in the pathogenesis of the disease (Table 2). This was strongly supported by a study that reported associated increase of IgM antibodies against TSST-1, streptococcal pyogenic exotoxin A and staphylococcal enterotoxin A (Matsubara & Fukaya, 2007). However, an earlier multicentre, prospective study detected no difference in the isolation of superantigen-producing bacteria between patients with the disease and febrile controls, thus complicating the matter further (Leung et al., 2002). On the other hand, bacterial toxins'-induced clonal expansion of T-cell receptors V $\beta$ 2 and V $\beta$ 8 is found among a subset of patients at the early stages of disease. This expansion seems to withdraw during the convalescent phase and may be responsible for the non specific T-cell activation that can lead to massive cytokine release and the development of KD (Abe et al., 1992; Brogan et al., 2008).

Another hypothesis for the etiology of KD involves the implication of an environmental cause, such as pesticides, chemicals, heavy metals, toxins and pollutants. However, poisoning with environmental agents does not usually manifest acutely and is the result of chronic exposure. Nonetheless, some studies correlate KD to recent exposure to freshly shampooed carpets, habitation near a body of stagnant water and the use of a humidifier (Rauch et al., 1991; Treadwell et al., 2002).

	Kawasaki disease	Scarlet fever	Toxic shock syndrome
Age at onset	<5 years of age	>4 years of age	90% girls reaching the menstrual age
Epidemic	+	+	-
Cause	unknown	A streptococcal pyrogenic exotoxin (SPE- A, B,C)	Staphylococcus enterotoxin (TSST-1)
Features of rash	Polymorphous rash	Diffuse erythema	Diffuse erythema
Conjunctival injection	+	-	+
Labial and oral hyperemia	Whole area	Localized to pharynx, soft palate	Whole area
Cervical lymphadenopathy	+	+	-
Strawberry tongue	+	+	+
Erythema of the palms and soles	+	+	+
Palmar desquamation	+	+	+
Recurrence	3 - 4 %	rare	30,00%
Shock or hypotension	-	-	+
Coronary arteriitis	+	-	-

Table 2. Comparison of clinical features of Kawasaki disease, Scarlet fever, and Toxic shock syndrome

Other researchers have found evidence of an oligoclonal antibody response, suggesting that the disease is elicited by a conventional antigen rather than a superantigen (Rowley et al., 2001).

The predilection of the disease for children either living in Asia or being of Asian ancestry as well as the relatively higher recurrence within families point towards a genetic predisposition for developing KD (Caquard et al., 2006; Uehara et al., 2003). In Japan, the relative risk of developing the disease among siblings is 10, and it reaches to 13 when referring to twins (Harada et al., 1986). Several studies have been conducted, trying to link susceptibility to KD or disease outcome to genetic polymorphisms (Ahn et al., 2003; Burns et al., 2005; Furuno et al., 2004; Sato et al., 2009). However, most of these studies have been carried out on single small cohorts of KD patients and findings were reported without validation in additional case-control studies. Other limitations include the small scale number of alleles examined, control and sample populations heterogeneity that complicates comparison and the existence of silent undiagnosed cases within the control group. As opposed to candidate gene studies, genome-wide studies, which search for disease causing

mutations within the whole genome, seem very promising. One such recent study, has identified inositol 1,4,5-trisphosphate 3-kinase C (ITPK-C) gene as a susceptibility gene for KD (Onouchi et al., 2008). A functional single nucleotide polymorphism was recognized and associated with disease development but also with increased risk for the formation of coronary artery lesions. This polymorphism is shown to reduce splicing efficiency of ITPK-C mRNA. While ITPK-C is shown to act as a negative regulator of T-cell activation through the  $Ca^{2+}$ /nuclear factor of activated T-cells signal pathway, the reduced splicing efficiency may contribute to immune hyperreactivity and thus the pathogenesis of KD (Onouchi, 2010). Further research on the biological significance of ITPK-C in other immune or non-immune cells may lead to better understanding of the disease pathogenesis.

#### 4. Pathology

The histological findings of KD are consistent with those of a systemic vasculitis affecting medium sized arteries and veins to a lesser extent, with inflammatory lesions in virtually every organ. With the exception of arterial lesions, inflammatory lesions heal without residual changes (Amano et al., 1980; Masuda et al., 1986). Our understanding of the histopathological findings in KD is restricted due to the scarcity of study material for reasons such as the low mortality rate and the difficulties encountered upon sampling medium sized arteries, especially coronary arteries.

After the encounter of a genetically predisposed individual with the unknown trigger, an activation of mononuclear cells and platelets occurs (Jennette, 2002). The two latter cell populations interact with the endothelium that expresses surface adhesion molecules leading to margination of circulating cells, especially large mononuclear cells, lymphocytes and IgA plasma cells (Brown et al., 2001; Rowley et al., 2001). Activated endothelial cells also secrete monocyte chemoattractant protein 1 (MCP-1), which further attracts monocytes and vascular endothelial cell growth factor (VEGF), which increases vessel permeability (Asano & Ogawa, 2000; Maeno et al., 1998; Yasukawa et al., 2002). Afterwards, platelets adhere to the vascular wall, while inflammatory cells cross the endothelium, gather in the intima, and liberate proinflammatory molecules such as interleukins, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), and matrix metalloproteinases (MMP) (Eberhard et al., 1995; Gavin et al., 2003; Lin et al., 1992). Neutrophils release neutrophil elastase which destroys the internal elastic lamina and contributes to disruption of the extracellular matrix. Active inflammation is succeeded by progressive fibrosis and finally scar formation.

In the heart, perivasculitis and endarteritis of the three major coronary arteries are seen during the acute phase, followed by panvasculitis in the consequent two weeks period. Aneurysms, phlebitis, formation of intraluminal thrombi and potential pancarditis with lesions of the conduction system are also present during this phase of the disease. As the disease progresses, inflammation is replaced by granulation in the form of scarring, stenosis of major coronary arteries, fibrosis of the myocardium, coagulation necrosis, and endocardial fibroelastosis (Fujiwara & Hamashima, 1978).

Inflammatory changes of the lungs, spleen, lymph nodes and salivary glands remain for more than 61 days from the onset of the disease, while in other organs these changes resolve much earlier. A predilection of KD for duct systems such as the prostate, pancreas, bile ducts and salivary glands has also been documented. However, in contrast to the irreversible changes that may occur in the cardiovascular system, histological changes on other parts of the body seem to fully recover after the convalescent phase of the disease (Amano et al., 1980).

The histological findings in KD strongly resemble polyarteriitis nodosa, and even though fine differences between the two illnesses do exist, differential diagnosis can only be made clinically. Most importantly, KD manifests with lymphadenopathy, which is usually absent in patients with polyarteritis nodosa (Jennette, 2002).

## 5. Diagnosis & clinical features

Signs and symptoms of KD develop over the first ten days of the illness and then gradually disappear spontaneously in most patients. In 20–25 % of the cases the disease is complicated by coronary artery lesions that may remain silent and diagnosed only years later, after the occurrence of a myocardial infarction episode or sudden death (Burns et al., 1996; Kato et al., 1992). The disease may be separated in three phases according to its clinical presentation. The acute phase, which may last 7-14 days, the sub-acute phase from the 10th to the 24th day of the disease, and finally the convalescent phase, typically lasting 6-8 weeks. Diagnosis of the disease during the acute phase is of utmost significance, as treatment with high dose of intravenous immunoglobulin within the first 10 days of onset reduces the risk of coronary artery lesions (Newburger et al., 1986, 1991). However, diagnosis of the disease is quite challenging, first because it remains clinically silent for some time, and secondly because there is no specific diagnostic test available. Aside from key elements of the history and physical examination, as well as indications based on laboratory markers of inflammation, the disease is presently diagnosed by the use of a case definition created for epidemiological surveys in Japan. The diagnostic criteria for complete and incomplete KD are presented in Table 3 and Table 4 respectively.

<ul style="list-style-type: none"> <li>a. Fever lasting for at least 5 days</li> <li>b. Presence of 4 of the following 5 conditions:                             <ul style="list-style-type: none"> <li>1. Bilateral conjunctival injection</li> <li>2. Changes of the mucous membranes of the upper respiratory tract: injected pharynx, injected or/and dry fissured lips, strawberry tongue</li> <li>3. Polymorphous rash, primarily truncal.</li> <li>4. Changes of the extremities such as peripheral edema, peripheral erythema, and periungual desquamation.</li> <li>5. Cervical lymphadenopathy.</li> </ul> </li> <li>c. Absence of any other reasonable explanation for the illness.</li> </ul>
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Table 3. Diagnostic criteria for complete Kawasaki disease

<ul style="list-style-type: none"> <li>a. Fever lasting for at least 5 days.</li> <li>b. At least 2 of the 5 clinical criteria for Kawasaki disease (Table 3: B<sub>1-5</sub>).</li> <li>c. Absence of any other sensible explanation for the illness.</li> <li>d. Laboratory findings, consistent with severe systemic inflammation.</li> </ul>
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Table 4. Diagnostic criteria for incomplete/ atypical Kawasaki disease

Although according to the criteria diagnosis requires a minimum of 5 days of fever, many experts prefer to treat classic KD earlier than the 5th day. The reason is that the case definition of KD is of questionable value as a clinical tool (Stapp & Marshall, 2002; Witt et

al.,1999). A broader definition of the disease would ensure identification of all patients who could benefit from intravenous immunoglobulin treatment. It is very common that the criteria for diagnosis of KD are not all present at the same time during the course of the illness (Newburger & Fulton, 2004). Patients with an inflammatory disorder that did not meet all the clinical criteria but with echocardiographic abnormalities of the coronary arteries have been identified. It should also be noted that 5 of the patients in Kawasaki's original report of 50 patients did not fulfill the current criteria for the diagnosis of the disease (Burns, 2002).

The lack of a specific and sensitive diagnostic test remains a great obstacle in the identification of all patients with KD. Besides the possibility that the illness may be underdiagnosed, there is an almost equally high chance that the disease is overdiagnosed since clinicians use non specific laboratory markers of inflammation to support their diagnosis. Thus, differential diagnosis among diseases that require different treatment remains a challenge (Table 5).

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Scarlet fever</li> <li>• Toxic shock syndrome (TSS)</li> <li>• Staphylococcal scalded skin syndrome (SSSS)</li> <li>• Measles and other febrile viral exanthems</li> <li>• Drug reactions</li> <li>• Steven - Johnson's syndrome</li> <li>• Juvenile rheumatoid arthritis</li> </ul> |
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Table 5. Selected differential diagnosis of Kawasaki disease

Acknowledgement of the protective role that early administration of intravenous immunoglobulin may play in the disease has placed a significant burden on clinicians to consider diagnosis in patients with unexplained fever with rash. Certain features of KD that may potentially deceive physicians include sterile pyuria misdiagnosed as urinary tract infection, cerebrospinal fluid (CSF) pleiocytosis misdiagnosed as aseptic meningitis, rash that may resemble a viral or drug side-effect sign, and cervical lymphadenopathy that is often confused with bacterial adenitis ( Dengler et al., 1998; Wu et al, 2005).

The clinical symptoms upon presentation of the disease for the 34 hospitalized cases identified in our hospital between the years 1989 and 2005, are shown in Table 6. The predominant symptom was -as expected - fever with an average duration of 7,8 days. Other symptoms in decreasing order of frequency were rash, desquamation, conjunctivitis, lymphadenitis, fissured lips, glossitis, edema of the extremities, gastrointestinal abnormalities and arthritis. Aneurysms were identified in only 5 cases, and while tachycardia was absent in all cases, a 1<sup>st</sup> degree AV block was noted in 1 child.

Laboratory indices at the time of entrance were suggestive of a generalized activation of the inflammatory system. Average white blood cell (WBC) count was 16.193 cells/ $\mu$ l, average erythrocyte sedimentation rate (ESR) was 74.7 mm, average level of C-reactive protein (CRP) was 120,2 mg/l and average platelet count was 45.700/ $\mu$ l. Liver transaminases (aspartate aminotransferase, AST and alanine aminotransferase, ALT) were elevated in only 3 of the children. Urine analysis revealed the existence of aseptic pyuria in a 76,5% of the patients. An immune workup was performed for 10 of the children and is shown in Table 7. Finally, level of  $\alpha$ 1 - antithrypsin was tested in 3 cases and was found to be elevated in all three of them.



Clinical symptoms	Number of patients	% of patients
1. fever	34	100
2. rash	33	97,1
3. desquamation	27	79,4
4. conjunctivitis	26	76,5
5. lymphadenitis	26	76,5
6. fissured lips	26	76,5
7. glossitis	14	41,2
8. edema of the extremities	11	32,4
9. aneurysms	5	14,7
10. gastrointestinal abnormalities	5	14,7
11. arrhythmia	1	2,9
12. arthritis	1	2,9

Table 6. Clinical presentation upon admission of the 34 cases of patients hospitalized for Kawasaki disease in "P & A Kyriakou" Children's Hospital in Athens, Greece between the years 1989 and 2005

	Number of patients with <b>normal titer</b>	Number of patients with <b>elevated titer</b>	Number of patients with <b>decreased titer</b>
IgG	3	3	4
IgM	3	7	-
IgA	6	4	-

Table 7. Immune workup of the ten patients that underwent the examination in "P & A Kyriakou" Children's Hospital in Athens, Greece between the years 1989 and 2005.

Even if the underlying cause remains unknown, there is an ever increasing need for the development of a unique diagnostic test that can help in identification of the disease. Although non specific markers of inflammation such as serum procalcitonin, interleukin-18 (IL-18), WBC count, ESR, and CRP are all found elevated in KD, no association to the severity of the illness has yet been established (Mitani et al., 2005; Nomura et al., 2004; Okada et al., 2004). Unfortunately, the diagnosis of the disease currently depends largely on increased clinical awareness.

## 6. Cardiovascular complications

Kawasaki disease has become the leading cause of acquired heart disease among children in the developed world, even surpassing the impact of rheumatic fever in this respect. Twenty to 25% of untreated patients with KD develop coronary artery aneurysms and myocardial

infarction with an associated considerable morbidity and mortality (Taubert et al., 1994). Other cardiovascular complications related with the disease include coronary artery stenosis, myocarditis, pericarditis with effusion and mitral valvulitis (Akagi et al., 1990; Dajani et al., 1993). Cardiac imaging is hence very important in the evaluation of patients with suspected KD. Echocardiography is both a sensitive and specific method to recognize coronary artery aneurysms in the acute and subacute phase of the disease (Yoshikawa et al., 1979). Serial ultrasound studies can provide evidence of aneurysm formation, they may help evaluate left ventricular function as well as detect possible existence of pericardial effusion (McMorrow Tuohy et al., 2001; Scott et al., 1999). Doppler echocardiography can assist in the identification of mitral valve regurgitation and is also advisable in the presence of a pansystolic murmur upon auscultation. Morphological assessment of coronary arteries is of high significance, as the prognosis of aneurysms in patients with KD depends on the size and shape of the aneurysm. These features are best evaluated with three-dimensional echocardiography (Miyashita et al., 2007). Coronary artery aneurysms are characterized as small if less than 5 mm in internal diameter, medium if 5–8 mm, or giant if larger than 8 mm (Dayani et al., 1993, 1994). Fusiform aneurysms with a diameter of less than 8 mm have the best outcome, while giant aneurysms more than 8 mm have the worst. The latter is attributed to the fact that giant coronary aneurysms are highly probable to cause ischemic heart disease (Kamiya et al., 1995; Tataru & Kusakawa, 1987). On the contrary, small and medium diameter aneurysms have been reported to regress in approximately 50% of the cases and progress to stenosis in another 20% of patients (Kato et al., 1996). However, the value of echocardiographic detection of thrombi and coronary artery stenosis is questionable. In a selection of patients with KD, a series of other tests are recommended, aiming at better visualization of the coronary arteries. These include angiography, intravascular ultrasound, transesophageal echocardiography, magnetic resonance imaging, magnetic resonance angiography and ultrafast computed tomography (Greil et al., 2002; Naiser et al., 2008; Newburger et al., 2004; Suzuki et al., 1996). Interestingly, coronary artery lesions following KD may remain silent until the patient becomes 30 or even 40 years old. Especially patients without pathological findings in their echocardiogram during the acute and subacute phases of the disease usually remain clinically asymptomatic for at least a decade. To this end, a pediatric history of illness resembling KD should be sought in young adults presenting with myocardial infarction or sudden death (Burns et al., 1996; Kato et al., 1992).

Suggested risk factors for coronary artery formation include fever that endures even after intravenous immunoglobulin administration, elevated CRP, low hemoglobin, thrombocytopenia, hypoalbuminemia, hyponatremia, male sex and age under one year (Honkanen et al., 2003; Koren et al., 1986; Mori et al., 2002). A proposed stratification of patients according to the relative risk for developing myocardial ischemia is presented, in table 9 (Newburger et al., 2004).

## **7. Treatment**

### **7.1 Initial treatment**

Coronary artery aneurysms develop in 20 – 25% of patients left untreated. During the acute phase, the primary objective is to ascertain the diagnosis of the disease, provide supportive

Risk level	Pharmacological therapy	Follow - up & diagnostic tests	Invasive tests
1 (no coronary artery changes at any stage of illness)	None beyond first 6-8 weeks	Cardiovascular risk assessment, counseling every 5 years	-
2 (transient coronary artery ectasia disappears within first 6-8 weeks)	None beyond first 6-8 weeks	Cardiovascular risk assessment, counseling every 3-5 years	-
3 (1 small-to-medium coronary artery aneurysm/ major coronary artery)	Low-dose aspirin (3-5 mg/kg aspirin/day), at least until aneurysm regression is documented	ECHO+ECG, cardiovascular risk assesment, counseling annually. Stress test/ evaluation of myocardial perfusion scan every 2 years	Angiography, if noninvasive test suggests ischemia
4 (1 large or giant coronary artery aneurysm, or multiple or complex aneurysms in the same coronary artery, without obstruction)	Long-term antiplatelet therapy and warfarin (target INR 2.0-2.5) or low-molecular-weight heparin (target: antifactor Xa level 0.5-1.0 U/ml) should be combined in giant aneurysms.	ECHO+ECG twice annually. Stress test /evaluation of myocardial perfusion annually.	First angiography at 6-12 months or sooner if clinically indicated; repeated angiography if noninvasive test, clinical, or laboratory findings suggest ischemia; elective repeat angiography under some circumstances
5 (coronary artery obstruction)	Long-term low-dose aspirin. Warfarin or low-molecular-weight heparin if giant aneurysm persists. Use of beta blockers to reduce myocardial O <sub>2</sub> consumption should also be considered	ECHO+ECG twice annually. Stress test /evaluation of myocardial perfusion annually.	Angiography recommended to address therapeutic options

Table 9. Risk stratification for Kawasaki disease (ECHO: echocardiography, EKG electrocardiogram, INR: International normalized ratio)

care whenever needed (fluid and electrolytes), aim to attenuate the inflammatory process and prevent the formation of coronary artery aneurysms. Echocardiographic identification of coronary artery aneurysms not only redirects primary treatment plan, but also contributes to establishing the diagnosis of KD when there is absence of symptoms other than fever. It is thus suggested to consider echocardiography in a child with high fever of unknown etiology lasting more than 5 days and concurrent signs of generalized inflammation.

Intravenous immunoglobulin G is the cornerstone of treatment for KD during the acute phase. Several studies have shown that intravenous immunoglobulin G administration early in the course of the disease (before the 10th day from fever onset) reduces total duration of clinical symptoms as well as the incidence of coronary artery aneurysms (Durongpitsitkul et al., 1995; Furusho et al., 1984). It has been demonstrated that a single dose of 2 g/kg intravenous immunoglobulin G infused over 10–12 hours is more effective than multiple doses, and together with aspirin (Kato et al., 1996) now comprise the standard therapy in the USA, UK, Europe, Australia and many parts of Asia (Brogan et al., 2002). Although treatment should be instituted within the first ten days of illness, intravenous immunoglobulin G administration to children beyond the tenth day of illness is also recommended if they have either persistent fever without other explanation or aneurysms and ongoing systemic inflammation (Marasini et al., 1991; Newburger et al., 2004). The molecular basis for the anti-inflammatory action of intravenous immunoglobulin G is a field of extended research. Several mechanisms have been proposed including induction of immune inhibitory receptors such as FcγIII on macrophages (Samuelsson et al., 2001), blocked interaction between endothelial and natural killer (NK) cells, necrosis-like changes in morphologic features of neutrophils (Sugita et al., 2005), accelerated apoptosis of circulating neutrophils (Tsujiimoto et al., 2002) and down-regulation of genes expressed mainly by monocytes (Abe et al., 2005; Popper et al., 2007). Gamma globulin is a biological product manufactured from pooled donor plasma and adverse effects vary according to the product infused. Generally, adverse effects are considered mild, comprising of headache, myalgia, fever, chills, backache, chest pain, nausea, vomiting, as well as increased plasma viscosity. These effects are usually self-limited, rarely demanding cessation of therapy, although slowing down of the infusion may be required (Rosenfeld et al., 1995). Live virus vaccines should not be administered to patients for at least eleven months following treatment, due to reduced immunogenicity related to passive antibodies in the infused product.

Aspirin may also be administered in the acute phase of the disease in order to enhance the efficacy of intravenous immunoglobulin G. Currently, 80–100 mg/kg (divided in four doses) are administered in the acute inflammatory stage of the disease, while a single dose of 3–5 mg/kg is given when patients have been afebrile for 3–7 days. Aspirin may be continued indefinitely in children that have already developed coronary artery abnormalities. Despite the fact that aspirin has an important anti-inflammatory effect at high doses and an anti-platelet action at low doses, it does not shorten the frequency of coronary artery aneurysm complications (Terai & Shulman, 1997). The latter, along with aspirin's adverse effects and the risk for developing Reye's syndrome raise an important question regarding the value of exposing children with KD to high doses of aspirin.

Corticosteroids are the golden standard in the treatment of other forms of vasculitis. Nevertheless, their use in children with KD is limited (Shulman, 2003) even though they are found to suppress markers of inflammation and decrease total fever duration (Nonaka et al., 1995; Okada et al., 2003).

If initial therapy during the acute stage is successful, the primary objective at the subacute phase is to diminish platelet adhesion (usually by means of low dose aspirin administration), provision of supportive care when needed and monitoring patients in case of cardiovascular involvement. In both the subacute and convalescent phase, management plans are adjusted to coronary artery involvement and risk level, individualized for each patient (Newburger et al., 2004).

For the 34 cases included in our study, treatment comprised primarily of intravenous immunoglobulin G and aspirin as shown on Table 10. Aspirin was administered to 31 patients (91,2 %) during an average treatment duration of 5,7 days. Among children treated with aspirin, 23 continued with an antiplatelet dose (74,2%) after fever regression and only 1 patient had to discontinue aspirin treatment due to related hepatotoxicity. Twenty eight patients were treated with  $\gamma$ -globulin (82,4%) with an average treatment duration of 1,9 days. Additional therapy consisted of penicillin in 2 children, carbamazepine that was later replaced by sorbitole in 1 child, clindamycin in 1 and finally a combination of ampicillin and netilmycin in another 1 of the children. In terms of patients' management, there was also a case admitted to the intensive care unit of the hospital due to sepsis and multiple organ failure.

<b>Treatment with various doses of aspirin</b>		
dosage	Number of patients treated with aspirin	% of patients treated with aspirin
5 mg/ kg	3	9,6
60 mg/ kg	3	9,6
80 mg/ kg	13	41,9
85 mg/ kg	1	3,2
100 mg/kg	11	35,5
<b>Treatment with intravenous immunoglobulin G</b>		
dosage	Number of patients treated with IVIG	% of patients treated with IVIG
1 g/ kg	2	3,6
2 g/ kg	19	67,9
400 mg/ kg/ 24 h	7	25

Table 10. Treatment of the patients hospitalized for Kawasaki disease in "P & A Kyriakou" Children's Hospital in Athens, Greece between the years 1989 and 2005

## 7.2 Treatment of persistent or recrudescant fever

About 10–15% of children with KD that are treated with high dose aspirin and 2 g/kg intravenous immunoglobulin G will not become afebrile (Burns et al., 1998). Fever that is not reduced 36 hours after the completion of the initial intravenous immunoglobulin G infusion is defined as persistent or recrudescant fever. This subgroup, consisting of unresponsive to

intravenous immunoglobulin G patients, is proved to be at a higher risk for developing coronary artery aneurysms (Newburger, 2000). Unfortunately, no studies have yet proven the efficacy of a specific secondary treatment. Clinicians should first re-evaluate initial diagnosis and then move to selection of an appropriate secondary treatment. Most experts recommend re-treatment with intravenous immunoglobulin G, while plasmapheresis and treatment with corticosteroids, cyclophosphamide, methotrexate and monoclonal antibodies against TNF-  $\alpha$  have also been suggested (Ahn & Kim, 2005; Al Mayouf, 2004; Mori et al., 1995; Weiss et al., 2004).

### 7.3 Treatment of cardiovascular complications

Treatment of coronary disease in patients with KD depends on the severity and extent of coronary involvement. Prevention of thrombosis and myointimal proliferation that leads to stenosis are the main objectives when managing patients with coronary aneurysms. Early coronary thrombosis occurs almost exclusively among patients with giant aneurysms (Takahashi, 1996). Unfortunately, no prospective data exist to guide clinicians towards the ideal plan; therefore, treatment of this subgroup of patients is still based on experts' recommendations. Prevention of thrombosis is accomplished by the administration of an antiplatelet or an anticoagulant agent, or most frequently by a combination of both.

Antiplatelet agents play a significant role in managing patients at every stage of the disease, since platelet activation is a fundamental component of thrombosis development in KD (Burns et al., 1984, Kuramochi et al., 2000). Therefore, low dose aspirin (3–5 mg/kg daily) is the backbone of therapy for asymptomatic patients with mild and stable disease. Use of other antiplatelet agents (such as clopidogrel or dipyridamole) alone or combined with aspirin, may be more effective in suppressing platelet activation with more advanced coronary abnormalities (O'Brien et al., 2000). Randomized trials are needed to establish the role of low molecular heparin, monoclonal antibodies against IIB/IIIA receptor and warfarin in the long term management of patients with giant aneurysms (Brogan et al., 2002; Williams et al., 2002).

In contrast to adult patients with aneurysms, the thrombus burden in children with KD is not related to the form of plaque instability and rupture (Kuramochi et al., 2000). Hence, randomized controlled trials involving children with coronary thrombosis are needed to set up the role of thrombolytic medication (traditionally used in adults) such as streptokinase, urokinase and tissue plasminogen activator.

Mechanical restoration of coronary blood flow is the other option in this group of patients that develop thrombosis. Coronary bypass grafting is the recommended surgical therapy upon evidence of reversible ischemia in stress imaging, if viable myocardium is present in the area of distribution of the affected vessel and when there is absence of coronary disease distal to the planned graft site (Kitamura et al., 1994). (Yoshikawa et al., 2000). Initially, the saphenous vein was used as the graft for this procedure; however, early failures in younger children led to the introduction of internal mammary arterial grafts (Kitamura et al., 1994). It was later found that patency rates of arterial grafts were higher as opposed to venal grafts. However, despite the encouraging results during the first decade after coronary artery bypass surgery, the arterial graft patency in later adult life is still unknown (Tsuda & Kitamura, 2004).

Catheter intervention (such as balloon angioplasty, stent implantation, rotational ablation and transluminal coronary revascularization) is indicated in the presence of ischemic

symptoms, reversible ischemia on stress testing and at least 75% stenosis of the left anterior descending coronary artery. Although the use of percutaneous coronary rotational ablation is still limited, this procedure may be the most appropriate catheter intervention for patients with KD. The advantage is the high success rate even among patients with calcified coronary artery stenoses (Ishii et al., 2002; Sugimura et al., 1997), which renders this method a potential therapeutic option also for postponing coronary artery bypass surgery (Lee et al., 2005). Contraindications to catheter intervention include vessels with multiple, ostial, or long-segment lesions (Akagi, 2011; Ishii et al., 2001).

## 8. Conclusion

Kawasaki disease is a systemic vasculitis of early childhood and comprises one of the leading causes of acquired heart disease in the western world. Although great efforts have been made in order to improve our understanding of the cause, pathogenesis and natural history of the disease, many of these aspects remain vague. Physical examination, laboratory markers of inflammation, and a case definition created for epidemiological surveys in Japan are the main tools currently available for the diagnosis of KD. Treatment with intravenous immunoglobulin in association with aspirin early in the course of the disease shortens the duration of symptoms and decreases the frequency of coronary artery abnormalities.

During the period 1989–2005, 34 children with KD were admitted in our hospital. Analysis of different clinical manifestations and laboratory indices showed similar results to other studies. All children presented with fever, while the other most common symptoms were conjunctivitis, lymphadenitis, fissured lips and desquamation. Laboratory analyses were suggestive of non-specific inflammation. Patients responded well to treatment with aspirin and  $\gamma$  – globulin, and with the exception of one patient that was admitted to the intensive care unit, all other children did not develop any severe complications.

Therapy of intravenous immunoglobulin-resistant KD remains obscure. What is the main concern, is the extent to which it is going to influence adult cardiovascular disease. Long term management of patients with KD is therefore very important and evidence-based approaches are required in order to define the best medical practice. Further research is also essential in elucidating the cause of the disease and developing high sensitivity and specificity diagnostic tests.

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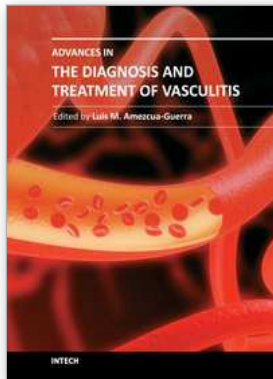
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## **Advances in the Diagnosis and Treatment of Vasculitis**

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This book represents the culmination of the efforts of a group of outstanding experts in vasculitis from all over the world, who have endeavored to draw themselves into this volume by keeping both the text and the accompanying figures and tables lucid and memorable. The book provides practical information about the screening approach to vasculitis by laboratory analysis, histopathology and advanced image techniques, current standard treatment along with new and more specific interventions including biologic agents, reparative surgery and experimental therapies, as well as miscellaneous issues such as the extra temporal manifestations of "temporal arteritis" or the diffuse alveolar hemorrhage syndrome. The editor and each of the authors invite you to share this journey by one of the most exciting fields of the medicine, the world of Vasculitis.

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